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(30) Priority Data:				(74) Agents: MAKI, David, J. et al.; So 6300, 701 Fifth Avenue, Seattle,	eed and Berry LLP, Suite WA 98104-7092 (US).		
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(71) Applicant (for all designated States except US): CORIXA CORPORATION [US/US]; Suite 200, 1124 Columbia Street, Seattle, WA 98104 (US).

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(72) Inventors; and

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09/454,150

(75) Inventors/Applicants (for US only): XU, Jiangchun [US/US]; 15805 SE 43rd Place, Bellevue, WA 98006 (US). LODES, Michael, J. [US/US]; 9223 - 36th Avenue SW, Seattle, WA 98126 (US). SECRIST, Heather [US/US]; 3844 -35th Avenue West, Seattle, WA 98199 (US). BENSON, Darin, R. [US/US]; 723 N. 48th Street, Seattle, WA 98104 (US). MEAGHER, Madeleine, Joy [US/US]; 3819 Interlake Avenue N., Seattle, WA 98103 (US). STOLK. John [US/US]; 7436 NE 144th Place, Bothell, WA 98011

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(57) Abstract

Compositions and methods for the therapy and diagnosis of cancer, such as colon cancer, are disclosed. Compositions may comprise one or more colon tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a colon tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as colon cancer. Diagnostic methods based on detecting a colon tumor protein, or mRNA encoding such a protein, in a sample are also provided.

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COMPOUNDS FOR IMMUNOTHERAPY AND DIAGNOSIS OF COLON CANCER AND METHODS FOR THEIR USE

TECHNICAL FIELD

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The present invention relates generally to therapy and diagnosis of cancer, such as colon cancer. The invention is more specifically related to polypeptides comprising at least a portion of a colon tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in vaccines and pharmaceutical compositions for prevention and treatment of colon cancer, and for the diagnosis and monitoring of such cancers.

BACKGROUND OF THE INVENTION

Cancer is a significant health problem throughout the world. Although advances have been made in detection and therapy of cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Current therapies, which are generally based on a combination of chemotherapy or surgery and radiation, continue to prove inadequate in many patients.

Colon cancer is the second most frequently diagnosed malignancy in the United States as well as the second most common cause of cancer death. An estimated 95,600 new cases of colon cancer will be diagnosed in 1998, with an estimated 47,700 deaths. The five-year survival rate for patients with colorectal cancer detected in an early localized stage is 92%; unfortunately, only 37% of colorectal cancer is diagnosed at this stage. The survival rate drops to 64% if the cancer is allowed to spread to adjacent organs or lymph nodes, and to 7% in patients with distant metastases.

The prognosis of colon cancer is directly related to the degree of penetration of the tumor through the bowel wall and the presence or absence of nodal involvement, consequently, early detection and treatment are especially important. Currently, diagnosis is aided by the use of screening assays for fecal occult blood, sigmoidoscopy, colonoscopy and double contrast barium enemas. Treatment regimens are determined by the type and stage of the cancer, and include surgery, radiation therapy and/or chemotherapy. Recurrence following surgery (the most common form of therapy) is a major problem and is often the

ultimate cause of death. In spite of considerable research into therapies for the disease, colon cancer remains difficult to diagnose and treat. In spite of considerable research into therapies for these and other cancers, colon cancer remains difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for detecting and treating such cancers. The present invention fulfills these needs and further provides other related advantages.

SUMMARY OF THE INVENTION

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Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as colon cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a colon tumor protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in SEQ ID NO: 1-121, 123-197 and 205-486; (b) variants of a sequence recited in SEQ ID NO: 1-121, 123-197 and 205-486; and (c) complements of a sequence of (a) or (b).

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of a colon tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, vaccines are provided. Such vaccines comprise a polypeptide or polynucleotide as described above and an immunostimulant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a colon tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, vaccines are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

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The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with an immunostimulant.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a colon tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a colon tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under

conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

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The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a colon tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expresses such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be colon cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a)

contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a colon tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a colon tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached figures. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

SEQUENCE IDENTIFIERS

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SEQ ID NO: 1 is a first determined cDNA sequence for Contig 1, showing homology to Neutrophil Gelatinase Associated Lipocalin.

SEQ ID NO: 2 is the determined cDNA sequence for Contig 2, showing no significant homology to any known genes.

SEQ ID NO: 3 is the determined cDNA sequence for Contig 4, showing homology to Carcinoembryonic antigen.

SEQ ID NO: 4 is the determined cDNA sequence for Contig 5, showing homology to Carcinoembryonic antigen.

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SEQ ID NO: 5 is the determined cDNA sequence for Contig 9, showing homology to Carcinoembryonic antigen.

SEQ ID NO: 6 is the determined cDNA sequence for Contig 52, showing homology to Carcinoembryonic antigen.

SEQ ID NO: 7 is the determined cDNA sequence for Contig 6, showing homology to Villin.

SEQ ID NO: 8 is the determined cDNA sequence for Contig 8, showing no significant homology to any known genes.

SEQ ID NO: 9 is the determined cDNA sequence for Contig 10, showing homology to Transforming Growth Factor (BIGH3).

SEQ ID NO: 10 is the determined cDNA sequence for Contig 19, showing homology to Transforming Growth Factor (BIGH3).

SEQ ID NO: 11 is the determined cDNA sequence for Contig 21, showing homology to Transforming Growth Factor (BIGH3).

SEQ ID NO: 12 is the determined cDNA sequence for Contig 11, showing homology to CO-029.

SEQ ID NO: 13 is the determined cDNA sequence for Contig 55, showing homology to CO-029.

SEQ ID NO: 14 is the determined cDNA sequence for Contig 12, showing homology to Chromosome 17, clone hRPC.1171_I_10, also referred to as C798P.

SEQ ID NO: 15 is the determined cDNA sequence for Contig 13, showing no significant homology to any known gene.

SEQ ID NO: 16 is the determined cDNA sequence for Contig 14, also referred to as 14261, showing no significant homology to any known gene.

SEQ ID NO: 17 is the determined cDNA sequence for Contig 15, showing homology to Ets-Related Transcription Factor (ERT).

SEQ ID NO: 18 is the determined cDNA sequence for Contig 16, showing homology to Chromosome 5, PAC clone 228g9 (LBNL H142).

SEQ ID NO: 19 is the determined cDNA sequence for Contig 24, showing homology to Chromosome 5, PAC clone 228g9 (LBNL H142).

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SEQ ID NO: 20 is the determined cDNA sequence for Contig 17, showing homology to Cytokeratin.

SEQ ID NO: 21 is the determined cDNA sequence for Contig 18, showing homology to L1-Cadherin.

SEQ ID NO: 22 is the determined cDNA sequence for Contig 20, showing no significant homology to any known gene.

SEQ ID NO: 23 is the determined cDNA sequence for Contig 22, showing homology to Bumetanide-sensitive Na-K-Cl cotransporter (NKCCl).

SEQ ID NO: 24 is the determined cDNA sequence for Contig 23, showing no significant homology to any known gene.

SEQ ID NO: 25 is the determined cDNA sequence for Contig 25, showing homology to Macrophage Inflammatory Protein 3 alpha.

SEQ ID NO: 26 is the determined cDNA sequence for Contig 26, showing homology to Laminin.

SEQ ID NO: 27 is the determined cDNA sequence for Contig 48, showing homology to Laminin.

SEQ ID NO: 28 is the determined cDNA sequence for Contig 27, showing homology to Mytobularin (MTM1).

SEQ ID NO: 29 is the determined cDNA sequence for Contig 28, showing homology to Chromosome 16 BAC clone CIT987SK-A-363E6.

SEQ ID NO: 30 is the determined cDNA sequence for Contig 29, also referred to as C751P and 14247, showing no significant homology to any known gene, but partial homology to Rat GSK-3β-interacting protein Axil homolog.

SEQ ID NO: 31 is the determined cDNA sequence for Contig 30, showing homology to Zinc Finger Transcription Factor (ZNF207).

SEQ ID NO: 32 is the determined cDNA sequence for Contig 31, showing no significant homology to any known gene, but partial homology to Mus musculus GOB-4 homolog.

SEQ ID NO: 33 is the determined cDNA sequence for Contig 35, showing no significant homology to any known gene, but partial homology to Mus musculus GOB-4 homolog.

SEQ ID NO: 34 is the determined cDNA sequence for Contig 32, showing no significant homology to any known gene.

SEQ ID NO: 35 is the determined cDNA sequence for Contig 34, showing homology to Desmoglein 2.

SEQ ID NO: 36 is the determined cDNA sequence for Contig 36, showing no significant homology to any known gene.

SEQ ID NO: 37 is the determined cDNA sequence for Contig 37, showing homology to Putative Transmembrane Protein.

SEQ ID NO: 38 is the determined cDNA sequence for Contig 38, also referred to as C796P and 14219, showing no significant homology to any known gene.

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SEQ ID NO: 39 is the determined cDNA sequence for Contig 40, showing homology to Nonspecific Cross-reacting Antigen.

SEQ ID NO: 40 is the determined cDNA sequence for Contig 41, also referred to as C799P and 14308, showing no significant homology to any known gene.

SEQ ID NO: 41 is the determined cDNA sequence for Contig 42, also referred to as C794P and 14309, showing no significant homology to any known gene.

SEQ ID NO: 42 is the determined cDNA sequence for Contig 43, showing homology to Chromosome 1 specific transcript KIAA0487.

SEQ ID NO: 43 is the determined cDNA sequence for Contig 45, showing homology to hMCM2.

SEQ ID NO: 44 is the determined cDNA sequence for Contig 46, showing homology to ETS2.

SEQ ID NO: 45 is the determined cDNA sequence for Contig 49, showing homology to Pump-1.

- SEQ ID NO: 46 is the determined cDNA sequence for Contig 50, also referred to as C792P and 18323, showing no significant homology to any known gene.
- SEQ ID NO: 47 is the determined cDNA sequence for Contig 51, also referred to as C795P and 14317, showing no significant homology to any known gene.
- SEQ ID NO: 48 is the determined cDNA sequence for 11092, showing no significant homology to any known gene.

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- SEQ ID NO: 49 is the determined cDNA sequence for 11093, showing no significant homology to any known gene.
- SEQ ID NO: 50 is the determined cDNA sequence for 11094, showing homology

 Human Putative Enterocyte Differentiation Protein.
 - SEQ ID NO: 51 is the determined cDNA sequence for 11095, showing homology to Human Transcriptional Corepressor hKAP1/TIF1B mRNA.
 - SEQ ID NO: 52 is the determined cDNA sequence for 11096, showing no significant homology to any known gene.
 - SEQ ID NO: 53 is the determined cDNA sequence for 11097, showing homology to Human Nonspecific Antigen.
 - SEQ ID NO: 54 is the determined cDNA sequence for 11098, showing no significant homology to any known gene.
 - SEQ ID NO: 55 is the determined cDNA sequence for 11099, showing homology to Human Pancreatic Secretory Inhibitor (PST) mRNA.
 - SEQ ID NO: 56 is the determined cDNA sequence for 11186, showing homology to Human Pancreatic Secretory Inhibitor (PST) mRNA.
 - SEQ ID NO: 57 is the determined cDNA sequence for 11101, showing homology to Human Chromosome X.
- SEQ ID NO: 58 is the determined cDNA sequence for 11102, showing homology to Human Chromosome X.
 - SEQ ID NO: 59 is the determined cDNA sequence for 11103, showing no significant homology to any known gene.
- SEQ ID NO: 60 is the determined cDNA sequence for 11174, showing no significant homology to any known gene.

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SEQ ID NO: 61 is the determined cDNA sequence for 11104, showing homology to Human mRNA for KIAA0154.

SEQ ID NO: 62 is the determined cDNA sequence for 11105, showing homology toHuman Apurinic/Apyrimidinic Endonuclease (hap1)mRNA.

SEQ ID NO: 63 is the determined cDNA sequence for 11106, showing homology toHuman Chromosome 12p13.

SEQ ID NO: 64 is the determined cDNA sequence for 11107, showing homology to Human 90 kDa Heat Shock Protein.

SEQ ID NO: 65 is the determined cDNA sequence for 11108, showing no significant homology to any known gene.

SEQ ID NO: 66 is the determined cDNA sequence for 11112, showing no significant homology to any known gene.

SEQ ID NO: 67 is the determined cDNA sequence for 11115, showing no significant homology to any known gene.

SEQ ID NO: 68 is the determined cDNA sequence for 11117, showing no significant homology to any known gene.

SEQ ID NO: 69 is the determined cDNA sequence for 11118, showing no significant homology to any known gene.

SEQ ID NO: 70 is the determined cDNA sequence for 11119, showing homology to Human Elongation Factor 1-alpha.

SEQ ID NO: 71 is the determined cDNA sequence for 11121, showing homology to Human Lamin B Receptor (LBR) mRNA.

SEQ ID NO: 72 is the determined cDNA sequence for 11122, showing homology to H. sapiens mRNA for Novel Glucocorticoid.

SEQ ID NO: 73 is the determined cDNA sequence for 11123, showing homology to H. sapiens mRNA for snRNP protein B.

SEQ ID NO: 74 is the determined cDNA sequence for 11124, showing homology to Human Cisplatin Resistance Associated Beta-protein.

SEQ ID NO: 75 is the determined cDNA sequence for 11127, showing homology to M. musculus Calumenin mRNA.

- SEQ ID NO: 76 is the determined cDNA sequence for 11128, showing homology to Human ras-related small GTP binding protein.
- SEQ ID NO: 77 is the determined cDNA sequence for 11130, showing homology to Human Cosmid U169d2.
- 5 SEQ ID NO: 78 is the determined cDNA sequence for 11131, showing homology to H. sapiens mRNA for protein homologous to Elongation 1-g.
 - SEQ ID NO: 79 is the determined cDNA sequence for 11134, showing no significant homology to any known gene.
- SEQ ID NO: 80 is the determined cDNA sequence for 11135, showing homology to H. sapiens Nieman-Pick (NPC1) mRNA.
 - SEQ ID NO: 81 is the determined cDNA sequence for 11137, showing homology to H. sapiens mRNA for Niecin b-chain.
 - SEQ ID NO: 82 is the determined cDNA sequence for 11138, showing homology to Human Endogenous Retroviral Protease mRNA.
- SEQ ID NO: 83 is the determined cDNA sequence for 11139, showing homology to H. sapiens mRNA for DMBT1 protein.
 - SEQ ID NO: 84 is the determined cDNA sequence for 11140, showing homology to H. sapiens ras GTPase activating-like protein.
- SEQ ID NO: 85 is the determined cDNA sequence for 11143, showing homology to Human Acidic Ribosomal Phosphoprotein PO mRNA.
 - SEQ ID NO: 86 is the determined cDNA sequence for 11144, showing homology to H. sapiens U21 mRNA.
 - SEQ ID NO: 87 is the determined cDNA sequence for 11145, showing homology to Human GTP-binding protein.
- SEQ ID NO: 88 is the determined cDNA sequence for 11148, showing homology to H. sapiens U21 mRNA.
 - SEQ ID NO: 89 is the determined cDNA sequence for 11151, showing no significant homology to any known gene.
- SEQ ID NO: 90 is the determined cDNA sequence for 11154, showing no significant homology to any known gene.

SEQ ID NO: 91 is the determined cDNA sequence for 11156, showing homology to H. sapiens Ribosomal Protein L27.

SEQ ID NO: 92 is the determined cDNA sequence for 11157, showing homology to H. sapiens Ribosomal Protein L27.

SEQ ID NO: 93 is the determined cDNA sequence for 11158, showing no significant homology to any known gene.

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SEQ ID NO: 94 is the determined cDNA sequence for 11162, showing homology to Ag-X antigen.

SEQ ID NO: 95 is the determined cDNA sequence for 11164, showing homology to
10 H. sapiens mRNA for Signal Recognition Protein sub14.

SEQ ID NO: 96 is the determined cDNA sequence for 11165, showing homology to Human PAC 204e5/127h14.

SEQ ID NO: 97 is the determined cDNA sequence for 11166, showing homology to Human mRNA for KIAA0108.

SEQ ID NO: 98 is the determined cDNA sequence for 11167, showing homology to H. sapiens mRNA for Neutrophil Gelatinase assct. Lipocalin.

SEQ ID NO: 99 is the determined cDNA sequence for 11168, showing no significant homology to any known gene.

SEQ ID NO: 100 is the determined cDNA sequence for 11172, showing no significant homology to any known gene.

SEQ ID NO: 101 is the determined cDNA sequence for 11175, showing no significant homology to any known gene.

SEQ ID NO: 102 is the determined cDNA sequence for 11176, showing homology to Human maspin mRNA.

SEQ ID NO: 103 is the determined cDNA sequence for 11177, showing homology to Human Carcinoembryonic Antigen.

SEQ ID NO: 104 is the determined cDNA sequence for 11178, showing homology to Human A-Tubulin mRNA.

SEQ ID NO: 105 is the determined cDNA sequence for 11179, showing homology to

Human mRNA for proton-ATPase-like protein.

- SEQ ID NO: 106 is the determined cDNA sequence for 11180, showing homology to Human HepG2 3' region cDNA clone hmd.
- SEQ ID NO: 107 is the determined cDNA sequence for 11182, showing homology to Human MHC homologous to Chicken B-Complex Protein.
- SEQ ID NO: 108 is the determined cDNA sequence for 11183, showing homology to Human High Mobility Group Box (SSRP1) mRNA.

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- SEQ ID NO: 109 is the determined cDNA sequence for 11184, showing no significant homology to any known gene.
- SEQ ID NO: 110 is the determined cDNA sequence for 11185, showing no significant homology to any known gene.
 - SEQ ID NO: 111 is the determined cDNA sequence for 11187, showing no significant homology to any known gene.
 - SEQ ID NO: 112 is the determined cDNA sequence for 11190, showing homology to Human Replication Protein A 70kDa.
- SEQ ID NO: 113 is the determined cDNA sequence for Contig 47, also referred to as C797P, showing homology to Human Chromosome X clone bWXD342.
 - SEQ ID NO: 114 is the determined cDNA sequence for Contig 7, showing homology to Equilibrative Nucleoside Transporter 2 (ent2).
- SEQ ID NO: 115 is the determined cDNA sequence for 14235.1, also referred to as C791P, showing homology to H. sapiens chromosome 21 derived BAC containing ets-2 gene.
 - SEQ ID NO: 116 is the determined cDNA sequence for 14287.2, showing no significant homology to any known gene, but some degree of homology to Putative Transmembrane Protein.
- SEQ ID NO: 117 is the determined cDNA sequence for 14233.1, also referred to as Contig 48, showing no significant homology to any known gene.
 - SEQ ID NO: 118 is the determined cDNA sequence for 14298.2, also referred to as C793P, showing no significant homology to any known gene.
- SEQ ID NO: 119 is the determined cDNA sequence for 14372, also referred to as

 Contig 44, showing no significant homology to any known gene.

SEQ ID NO: 120 is the determined cDNA sequence for 14295, showing homology to secreted cement gland protein XAG-2 homolog.

SEQ ID NO: 121 is the determined full-length cDNA sequence for a clone showing homology to Beta IG-H3.

SEQ ID NO: 122 is the predicted amino acid sequence for the clone of SEQ ID NO: 121.

SEQ ID NO: 123 is a longer determined cDNA sequence for C751P.

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SEQ ID NO: 124 is a longer determined cDNA sequence for C791P.

SEQ ID NO: 125 is a longer determined cDNA sequence for C792P.

SEQ ID NO: 126 is a longer determined cDNA sequence for C793P.

SEQ ID NO: 127 is a longer determined cDNA sequence for C794P.

SEQ ID NO: 128 is a longer determined cDNA sequence for C795P.

SEQ ID NO: 129 is a longer determined cDNA sequence for C796P.

SEQ ID NO: 130 is a longer determined cDNA sequence for C797P.

SEQ ID NO: 131 is a longer determined cDNA sequence for C798P.

SEO ID NO: 132 is a longer determined cDNA sequence for C799P.

SEQ ID NO: 133 is a first partial determined cDNA sequence for CoSub-3 (also known as 23569).

SEQ ID NO: 134 is a second partial determined cDNA sequence for CoSub-3 (also known as 23569).

SEQ ID NO: 135 is a first partial determined cDNA sequence for CoSub-13 (also known as 23579).

SEQ ID NO: 136 is a second partial determined cDNA sequence for CoSub-13 (also known as 23579).

SEQ ID NO: 137 is the determined cDNA sequence for CoSub-17 (also known as 23583).

SEQ ID NO: 138 is the determined cDNA sequence for CoSub-19 (also known as 23585).

SEQ ID NO: 139 is the determined cDNA sequence for CoSub-22 (also known as 23714).

SEQ ID NO: 140 is the determined cDNA sequence for CoSub-23 (also known as 23715).

- SEQ ID NO: 141 is the determined cDNA sequence for CoSub-26 (also known as 23717).
- 5 SEQ ID NO: 142 is the determined cDNA sequence for CoSub-33 (also known as 23724).
 - SEQ ID NO: 143 is the determined cDNA sequence for CoSub-34 (also known as 23725).
- SEQ ID NO: 144 is the determined cDNA sequence for CoSub-35 (also known as 23726).
 - SEQ ID NO: 145 is the determined cDNA sequence for CoSub-37 (also known as 23728).
 - SEQ ID NO: 146 is the determined cDNA sequence for CoSub-39 (also known as 23730).
- SEQ ID NO: 147 is the determined cDNA sequence for CoSub-42 (also known as 23766).
 - SEQ ID NO: 148 is the determined cDNA sequence for CoSub-44 (also known as 23768).
- SEQ ID NO: 149 is the determined cDNA sequence for CoSub-47 (also known as 20 23771).
 - SEQ ID NO: 150 is the determined cDNA sequence for CoSub-54 (also known as 23778).
 - SEQ ID NO: 151 is the determined cDNA sequence for CoSub-55 (also known as 23779).
- SEQ ID NO: 152 is the determined cDNA sequence for CT1 (also known as 24099).
 - SEO ID NO: 153 is the determined cDNA sequence for CT2 (also known as 24100).
 - SEQ ID NO: 154 is the determined cDNA sequence for CT3 (also known as 24101).
 - SEQ ID NO: 155 is the determined cDNA sequence for CT6 (also known as 24104).
 - SEO ID NO: 156 is the determined cDNA sequence for CT7 (also known as 24105).
- 30 SEQ ID NO: 157 is the determined cDNA sequence for CT12 (also known as 24110).
 - SEQ ID NO: 158 is the determined cDNA sequence for CT13 (also known as 24111).

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SEQ ID NO: 159 is the determined cDNA sequence for CT14 (also known as 24112).

SEQ ID NO: 160 is the determined cDNA sequence for CT15 (also known as 24113).

SEQ ID NO: 161 is the determined cDNA sequence for CT17 (also known as 24115).

SEQ ID NO: 162 is the determined cDNA sequence for CT18 (also known as 24116).

SEQ ID NO: 163 is the determined cDNA sequence for CT22 (also known as 23848).

SEQ ID NO: 164 is the determined cDNA sequence for CT24 (also known as 23849).

SEQ ID NO: 165 is the determined cDNA sequence for CT31 (also known as 23854).

SEQ ID NO: 166 is the determined cDNA sequence for CT34 (also known as 23856).

SEQ ID NO: 167 is the determined cDNA sequence for CT37 (also known as 23859).

SEQ ID NO: 168 is the determined cDNA sequence for CT39 (also known as 23860).

SEQ ID NO: 169 is the determined cDNA sequence for CT40 (also known as 23861).

SEQ ID NO: 170 is the determined cDNA sequence for CT51 (also known as 24130).

SEQ ID NO: 171 is the determined cDNA sequence for CT53 (also known as 24132).

SEQ ID NO: 172 is the determined cDNA sequence for CT63 (also known as 24595).

SEQ ID NO: 173 is the determined cDNA sequence for CT88 (also known as 24608).

SEQ ID NO: 174 is the determined cDNA sequence for CT92 (also known as 24800).

SEQ ID NO: 175 is the determined cDNA sequence for CT94 (also known as 24802).

SEQ ID NO: 176 is the determined cDNA sequence for CT102 (also known as 24805).

SEQ ID NO: 177 is the determined cDNA sequence for CT103 (also known as 20 24806).

SEQ ID NO: 178 is the determined cDNA sequence for CT111 (also known as 25520).

SEQ ID NO: 179 is the determined cDNA sequence for CT118 (also known as 25 25522).

SEQ ID NO: 180 is the determined cDNA sequence for CT121 (also known as 25523).

SEQ ID NO: 181 is the determined cDNA sequence for CT126 (also known as 25527).

30 SEQ ID NO: 182 is the determined cDNA sequence for CT135 (also known as 25534).

- SEQ ID NO: 183 is the determined cDNA sequence for CT140 (also known as 25537).
- SEQ ID NO: 184 is the determined cDNA sequence for CT145 (also known as 25542).
- 5 SEQ ID NO: 185 is the determined cDNA sequence for CT147 (also known as 25543).
 - SEQ ID NO: 186 is the determined cDNA sequence for CT148 (also known as 25544).
- SEQ ID NO: 187 is the determined cDNA sequence for CT502 (also known as 10 26420).
 - SEQ ID NO: 188 is the determined cDNA sequence for CT507 (also known as 26425).
 - SEQ ID NO: 189 is the determined cDNA sequence for CT521 (also known as 27366).
- SEQ ID NO: 190 is the determined cDNA sequence for CT544 (also known as 27375).
 - SEQ ID NO: 191 is the determined cDNA sequence for CT577 (also known as 27385).
- SEQ ID NO: 192 is the determined cDNA sequence for CT580 (also known as 20 27387).
 - SEQ ID NO: 193 is the determined cDNA sequence for CT594 (also known as 27540).
 - SEQ ID NO: 194 is the determined cDNA sequence for CT606 (also known as 27547).
- SEQ ID NO: 195 is the determined cDNA sequence for CT607 (also known as 27548).
 - SEQ ID NO: 196 is the determined cDNA sequence for CT599 (also known as 27903).
- SEQ ID NO: 197 is the determined cDNA sequence for CT632 (also known as a 27922).
 - SEQ ID NO: 198 is the predicted amino acid sequence for CT502 (SEQ ID NO: 187).

SEQ ID NO: 199 is the predicted amino acid sequence for CT507 (SEQ ID NO: 188). SEQ ID NO: 200 is the predicted amino acid sequence for CT521 (SEQ ID NO: 189). SEQ ID NO: 201 is the predicted amino acid sequence for CT544 (SEQ ID NO: 190). SEQ ID NO: 202 is the predicted amino acid sequence for CT606 (SEQ ID NO: 194). SEQ ID NO: 203 is the predicted amino acid sequence for CT607 (SEQ ID NO: 195). 5 SEQ ID NO: 204 is the predicted amino acid sequence for CT632 (SEQ ID NO: 197). SEQ ID NO: 205 is the determined cDNA sequence for clone 25244. SEQ ID NO: 206 is the determined cDNA sequence for clone 25245. SEQ ID NO: 207 is the determined cDNA sequence for clone 25246. 10 SEQ ID NO: 208 is the determined cDNA sequence for clone 25248. SEQ ID NO: 209 is the determined cDNA sequence for clone 25249. SEQ ID NO: 210 is the determined cDNA sequence for clone 25250. SEQ ID NO: 211 is the determined cDNA sequence for clone 25251. SEQ ID NO: 212 is the determined cDNA sequence for clone 25252. SEQ ID NO: 213 is the determined cDNA sequence for clone 25253. 15 SEO ID NO: 214 is the determined cDNA sequence for clone 25254. SEQ ID NO: 215 is the determined cDNA sequence for clone 25255. SEQ ID NO: 216 is the determined cDNA sequence for clone 25256. SEQ ID NO: 217 is the determined cDNA sequence for clone 25257. SEQ ID NO: 218 is the determined cDNA sequence for clone 25259. 20 SEO ID NO: 219 is the determined cDNA sequence for clone 25260. SEQ ID NO: 220 is the determined cDNA sequence for clone 25261. SEQ ID NO: 221 is the determined cDNA sequence for clone 25262. SEQ ID NO: 222 is the determined cDNA sequence for clone 25263. SEQ ID NO: 223 is the determined cDNA sequence for clone 25264. 25 SEQ ID NO: 224 is the determined cDNA sequence for clone 25265. SEQ ID NO: 225 is the determined cDNA sequence for clone 25266. SEQ ID NO: 226 is the determined cDNA sequence for clone 25267. SEQ ID NO: 227 is the determined cDNA sequence for clone 25268. 30 SEQ ID NO: 228 is the determined cDNA sequence for clone 25269. SEQ ID NO: 229 is the determined cDNA sequence for clone 25271.

SEQ ID NO: 230 is the determined cDNA sequence for clone 25272. SEQ ID NO: 231 is the determined cDNA sequence for clone 25273. SEQ ID NO: 232 is the determined cDNA sequence for clone 25274. SEQ ID NO: 233 is the determined cDNA sequence for clone 25275. 5 SEQ ID NO: 234 is the determined cDNA sequence for clone 25276. SEQ ID NO: 235 is the determined cDNA sequence for clone 25277. SEO ID NO: 236 is the determined cDNA sequence for clone 25278. SEQ ID NO: 237 is the determined cDNA sequence for clone 25280. SEQ ID NO: 238 is the determined cDNA sequence for clone 25281. SEO ID NO: 239 is the determined cDNA sequence for clone 25282. 10 SEQ ID NO: 240 is the determined cDNA sequence for clone 25283. SEQ ID NO: 241 is the determined cDNA sequence for clone 25284. SEQ ID NO: 242 is the determined cDNA sequence for clone 25285. SEO ID NO: 243 is the determined cDNA sequence for clone 25286. SEQ ID NO: 244 is the determined cDNA sequence for clone 25287. 15 SEQ ID NO: 245 is the determined cDNA sequence for clone 25288. SEQ ID NO: 246 is the determined cDNA sequence for clone 25289. SEQ ID NO: 247 is the determined cDNA sequence for clone 25290. SEQ ID NO: 248 is the determined cDNA sequence for clone 25291. SEQ ID NO: 249 is the determined cDNA sequence for clone 25292. 20 SEQ ID NO: 250 is the determined cDNA sequence for clone 25293. SEQ ID NO: 251 is the determined cDNA sequence for clone 25294. SEQ ID NO: 252 is the determined cDNA sequence for clone 25295. SEO ID NO: 253 is the determined cDNA sequence for clone 25296. 25 SEQ ID NO: 254 is the determined cDNA sequence for clone 25297. SEQ ID NO: 255 is the determined cDNA sequence for clone 25418. SEQ ID NO: 256 is the determined cDNA sequence for clone 25419. SEQ ID NO: 257 is the determined cDNA sequence for clone 25420. SEQ ID NO: 258 is the determined cDNA sequence for clone 25421. SEQ ID NO: 259 is the determined cDNA sequence for clone 25422. 30 SEQ ID NO: 260 is the determined cDNA sequence for clone 25423.

SEQ ID NO: 261 is the determined cDNA sequence for clone 25424. SEQ ID NO: 262 is the determined cDNA sequence for clone 25426. SEQ ID NO: 263 is the determined cDNA sequence for clone 25427. SEQ ID NO: 264 is the determined cDNA sequence for clone 25428. 5 SEQ ID NO: 265 is the determined cDNA sequence for clone 25429. SEQ ID NO: 266 is the determined cDNA sequence for clone 25430. SEQ ID NO: 267 is the determined cDNA sequence for clone 25431. SEQ ID NO: 268 is the determined cDNA sequence for clone 25432. SEQ ID NO: 269 is the determined cDNA sequence for clone 25433. SEQ ID NO: 270 is the determined cDNA sequence for clone 25434. 10 SEQ ID NO: 271 is the determined cDNA sequence for clone 25435. SEQ ID NO: 272 is the determined cDNA sequence for clone 25436. SEQ ID NO: 273 is the determined cDNA sequence for clone 25437. SEQ ID NO: 274 is the determined cDNA sequence for clone 25438. SEQ ID NO: 275 is the determined cDNA sequence for clone 25439. 15 SEQ ID NO: 276 is the determined cDNA sequence for clone 25440. SEQ ID NO: 277 is the determined cDNA sequence for clone 25441. SEQ ID NO: 278 is the determined cDNA sequence for clone 25442. SEQ ID NO: 279 is the determined cDNA sequence for clone 25443. 20 SEQ ID NO: 280 is the determined cDNA sequence for clone 25444. SEQ ID NO: 281 is the determined cDNA sequence for clone 25445. SEQ ID NO: 282 is the determined cDNA sequence for clone 25446. SEQ ID NO: 283 is the determined cDNA sequence for clone 25447. SEQ ID NO: 284 is the determined cDNA sequence for clone 25448. 25 SEQ ID NO: 285 is the determined cDNA sequence for clone 25844. SEQ ID NO: 286 is the determined cDNA sequence for clone 25845. SEQ ID NO: 287 is the determined cDNA sequence for clone 25846. SEQ ID NO: 288 is the determined cDNA sequence for clone 25847. SEQ ID NO: 289 is the determined cDNA sequence for clone 25848. 30 SEQ ID NO: 290 is the determined cDNA sequence for clone 25850. SEQ ID NO: 291 is the determined cDNA sequence for clone 25851.

SEQ ID NO: 292 is the determined cDNA sequence for clone 25852. SEQ ID NO: 293 is the determined cDNA sequence for clone 25853. SEQ ID NO: 294 is the determined cDNA sequence for clone 25854. SEQ ID NO: 295 is the determined cDNA sequence for clone 25855. SEQ ID NO: 296 is the determined cDNA sequence for clone 25856. 5 SEQ ID NO: 297 is the determined cDNA sequence for clone 25857. SEQ ID NO: 298 is the determined cDNA sequence for clone 25858. SEQ ID NO: 299 is the determined cDNA sequence for clone 25859. SEQ ID NO: 300 is the determined cDNA sequence for clone 25860. SEQ ID NO: 301 is the determined cDNA sequence for clone 25861. 10 SEQ ID NO: 302 is the determined cDNA sequence for clone 25862. SEQ ID NO: 303 is the determined cDNA sequence for clone 25863. SEQ ID NO: 304 is the determined cDNA sequence for clone 25864. SEQ ID NO: 305 is the determined cDNA sequence for clone 25865. SEQ ID NO: 306 is the determined cDNA sequence for clone 25866. 15 SEO ID NO: 307 is the determined cDNA sequence for clone 25867. SEO ID NO: 308 is the determined cDNA sequence for clone 25868. SEQ ID NO: 309 is the determined cDNA sequence for clone 25869. SEQ ID NO: 310 is the determined cDNA sequence for clone 25870. SEQ ID NO: 311 is the determined cDNA sequence for clone 25871. 20 SEQ ID NO: 312 is the determined cDNA sequence for clone 25872. SEQ ID NO: 313 is the determined cDNA sequence for clone 25873. SEQ ID NO: 314 is the determined cDNA sequence for clone 25875. SEQ ID NO: 315 is the determined cDNA sequence for clone 25876. 25 SEQ ID NO: 316 is the determined cDNA sequence for clone 25877. SEQ ID NO: 317 is the determined cDNA sequence for clone 25878. SEQ ID NO: 318 is the determined cDNA sequence for clone 25879. SEQ ID NO: 319 is the determined cDNA sequence for clone 25880. SEO ID NO: 320 is the determined cDNA sequence for clone 25881. SEQ ID NO: 321 is the determined cDNA sequence for clone 25882. 30 SEO ID NO: 322 is the determined cDNA sequence for clone 25883.

SEQ ID NO: 323 is the determined cDNA sequence for clone 25884. SEQ ID NO: 324 is the determined cDNA sequence for clone 25885. SEQ ID NO: 325 is the determined cDNA sequence for clone 25886. SEQ ID NO: 326 is the determined cDNA sequence for clone 25887. 5 SEQ ID NO: 327 is the determined cDNA sequence for clone 25888. SEQ ID NO: 328 is the determined cDNA sequence for clone 25889. SEQ ID NO: 329 is the determined cDNA sequence for clone 25890. SEQ ID NO: 330 is the determined cDNA sequence for clone 25892. SEQ ID NO: 331 is the determined cDNA sequence for clone 25894. SEQ ID NO: 332 is the determined cDNA sequence for clone 25895. 10 SEQ ID NO: 333 is the determined cDNA sequence for clone 25896. SEQ ID NO: 334 is the determined cDNA sequence for clone 25897. SEQ ID NO: 335 is the determined cDNA sequence for clone 25899. SEQ ID NO: 336 is the determined cDNA sequence for clone 25900. 15 SEQ ID NO: 337 is the determined cDNA sequence for clone 25901. SEQ ID NO: 338 is the determined cDNA sequence for clone 25902. SEQ ID NO: 339 is the determined cDNA sequence for clone 25903. SEQ ID NO: 340 is the determined cDNA sequence for clone 25904. SEQ ID NO: 341 is the determined cDNA sequence for clone 25906. SEQ ID NO: 342 is the determined cDNA sequence for clone 25907. 20 SEQ ID NO: 343 is the determined cDNA sequence for clone 25908. SEQ ID NO: 344 is the determined cDNA sequence for clone 25909. SEQ ID NO: 345 is the determined cDNA sequence for clone 25910. SEQ ID NO: 346 is the determined cDNA sequence for clone 25911. 25 SEQ ID NO: 347 is the determined cDNA sequence for clone 25912. SEQ ID NO: 348 is the determined cDNA sequence for clone 25913. SEQ ID NO: 349 is the determined cDNA sequence for clone 25914. SEQ ID NO: 350 is the determined cDNA sequence for clone 25915. SEQ ID NO: 351 is the determined cDNA sequence for clone 25916. 30 SEQ ID NO: 352 is the determined cDNA sequence for clone 25917. SEQ ID NO: 353 is the determined cDNA sequence for clone 25918.

SEQ ID NO: 354 is the determined cDNA sequence for clone 25919. SEQ ID NO: 355 is the determined cDNA sequence for clone 25920. SEQ ID NO: 356 is the determined cDNA sequence for clone 25921. SEQ ID NO: 357 is the determined cDNA sequence for clone 25922. SEQ ID NO: 358 is the determined cDNA sequence for clone 25924. SEQ ID NO: 359 is the determined cDNA sequence for clone 25925. SEQ ID NO: 360 is the determined cDNA sequence for clone 25926. SEQ ID NO: 361 is the determined cDNA sequence for clone 25927. SEQ ID NO: 362 is the determined cDNA sequence for clone 25928. SEQ ID NO: 363 is the determined cDNA sequence for clone 25929. SEQ ID NO: 364 is the determined cDNA sequence for clone 25930. SEQ ID NO: 365 is the determined cDNA sequence for clone 25931. SEQ ID NO: 366 is the determined cDNA sequence for clone 25932. SEQ ID NO: 367 is the determined cDNA sequence for clone 25933. SEQ ID NO: 368 is the determined cDNA sequence for clone 25934. SEO ID NO: 369 is the determined cDNA sequence for clone 25935. SEQ ID NO: 370 is the determined cDNA sequence for clone 25936. SEQ ID NO: 371 is the determined cDNA sequence for clone 25939. SEQ ID NO: 372 is the determined cDNA sequence for clone 32016. SEQ ID NO: 373 is the determined cDNA sequence for clone 32021. SEQ ID NO: 374 is the determined cDNA sequence for clone 31993. SEQ ID NO: 375 is the determined cDNA sequence for clone 31997. SEQ ID NO: 376 is the determined cDNA sequence for clone 31942. SEQ ID NO: 377 is the determined cDNA sequence for clone 31937. SEQ ID NO: 378 is the determined cDNA sequence for clone 31952. SEQ ID NO: 379 is the determined cDNA sequence for clone 31992. SEQ ID NO: 380 is the determined cDNA sequence for clone 31961. SEQ ID NO: 381 is the determined cDNA sequence for clone 31964. SEQ ID NO: 382 is the determined cDNA sequence for clone 32005. SEQ ID NO: 383 is the determined cDNA sequence for clone 31980. 30 SEQ ID NO: 384 is the determined cDNA sequence for clone 31940.

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SEQ ID NO: 385 is the determined cDNA sequence for clone 32004. SEQ ID NO: 386 is the determined cDNA sequence for clone 31956. SEQ ID NO: 387 is the determined cDNA sequence for clone 31934. SEQ ID NO: 388 is the determined cDNA sequence for clone 31998. SEQ ID NO: 389 is the determined cDNA sequence for clone 31973. 5 SEQ ID NO: 390 is the determined cDNA sequence for clone 31976. SEQ ID NO: 391 is the determined cDNA sequence for clone 31988. SEQ ID NO: 392 is the determined cDNA sequence for clone 31948. SEQ ID NO: 393 is the determined cDNA sequence for clone 32013. 10 SEQ ID NO: 394 is the determined cDNA sequence for clone 31986. SEQ ID NO: 395 is the determined cDNA sequence for clone 31954. SEQ ID NO: 396 is the determined cDNA sequence for clone 31987. SEQ ID NO: 397 is the determined cDNA sequence for clone 32029. SEQ ID NO: 398 is the determined cDNA sequence for clone 32028. 15 SEQ ID NO: 399 is the determined cDNA sequence for clone 32012. SEQ ID NO: 400 is the determined cDNA sequence for clone 31959. SEQ ID NO: 401 is the determined cDNA sequence for clone 32027. SEQ ID NO: 402 is the determined cDNA sequence for clone 31957. SEQ ID NO: 403 is the determined cDNA sequence for clone 31950. 20 SEQ ID NO: 404 is the determined cDNA sequence for clone 32011. SEQ ID NO: 405 is the determined cDNA sequence for clone 32022. SEQ ID NO: 406 is the determined cDNA sequence for clone 32014. SEQ ID NO: 407 is the determined cDNA sequence for clone 31963. SEQ ID NO: 408 is the determined cDNA sequence for clone 31989. 25 SEQ ID NO: 409 is the determined cDNA sequence for clone 32015. SEQ ID NO: 410 is the determined cDNA sequence for clone 32002. SEQ ID NO: 411 is the determined cDNA sequence for clone 31939. SEQ ID NO: 412 is the determined cDNA sequence for clone 32003. SEQ ID NO: 413 is the determined cDNA sequence for clone 31936. 30 SEQ ID NO: 414 is the determined cDNA sequence for clone 32007. SEQ ID NO: 415 is the determined cDNA sequence for clone 31965.

SEQ ID NO: 416 is the determined cDNA sequence for clone 31935. SEQ ID NO: 417 is the determined cDNA sequence for clone 32008. SEQ ID NO: 418 is the determined cDNA sequence for clone 31966. SEQ ID NO: 419 is the determined cDNA sequence for clone 32020. SEQ ID NO: 420 is the determined cDNA sequence for clone 31971. 5 SEQ ID NO: 421 is the determined cDNA sequence for clone 31977. SEQ ID NO: 422 is the determined cDNA sequence for clone 31985. SEQ ID NO: 423 is the determined cDNA sequence for clone 32023. SEQ ID NO: 424 is the determined cDNA sequence for clone 31981. 10 SEQ ID NO: 425 is the determined cDNA sequence for clone 32006. SEQ ID NO: 426 is the determined cDNA sequence for clone 31991. SEQ ID NO: 427 is the determined cDNA sequence for clone 31995. SEQ ID NO: 428 is the determined cDNA sequence for clone 32000. SEQ ID NO: 429 is the determined cDNA sequence for clone 31990. 15 SEQ ID NO: 430 is the determined cDNA sequence for clone 31946. SEQ ID NO: 431 is the determined cDNA sequence for clone 31938. SEQ ID NO: 432 is the determined cDNA sequence for clone 31941. SEQ ID NO: 433 is the determined cDNA sequence for clone 31982. SEQ ID NO: 434 is the determined cDNA sequence for clone 31996. 20 SEQ ID NO: 435 is the determined cDNA sequence for clone 32010. SEQ ID NO: 436 is the determined cDNA sequence for clone 31974. SEQ ID NO: 437 is the determined cDNA sequence for clone 31983. SEQ ID NO: 438 is the determined cDNA sequence for clone 31999. SEQ ID NO: 439 is the determined cDNA sequence for clone 31949. 25 SEQ ID NO: 440 is the determined cDNA sequence for clone 31947. SEQ ID NO: 441 is the determined cDNA sequence for clone 31994. SEQ ID NO: 442 is the determined cDNA sequence for clone 31958. SEQ ID NO: 443 is the determined cDNA sequence for clone 31975. SEQ ID NO: 444 is the determined cDNA sequence for clone 31984. SEQ ID NO: 445 is the determined cDNA sequence for clone 32024. 30 SEQ ID NO: 446 is the determined cDNA sequence for clone 31972.

SEQ ID NO: 447 is the determined cDNA sequence for clone 31943. SEQ ID NO: 448 is the determined cDNA sequence for clone 32018. SEQ ID NO: 449 is the determined cDNA sequence for clone 32026. SEO ID NO: 450 is the determined cDNA sequence for clone 32009. 5 SEQ ID NO: 451 is the determined cDNA sequence for clone 32019. SEO ID NO: 452 is the determined cDNA sequence for clone 32025. SEQ ID NO: 453 is the determined cDNA sequence for clone 31967. SEO ID NO: 454 is the determined cDNA sequence for clone 31968. SEO ID NO: 455 is the determined cDNA sequence for clone 31955. SEQ ID NO: 456 is the determined cDNA sequence for clone 31951. 10 SEO ID NO: 457 is the determined cDNA sequence for clone 31970. SEQ ID NO: 458 is the determined cDNA sequence for clone 31962. SEO ID NO: 459 is the determined cDNA sequence for clone 32001. SEO ID NO: 460 is the determined cDNA sequence for clone 31953. SEQ ID NO: 461 is the determined cDNA sequence for clone 31944. 15 SEQ ID NO: 462 is the determined cDNA sequence for clone 31825. SEO ID NO: 463 is the determined cDNA sequence for clone 31828. SEO ID NO: 464 is the determined cDNA sequence for clone 31830. SEQ ID NO: 465 is the determined cDNA sequence for clone 31841. SEO ID NO: 466 is the determined cDNA sequence for clone 31847. 20 SEO ID NO: 467 is the determined cDNA sequence for clone 31850. SEQ ID NO: 468 is the determined cDNA sequence for clone 31852. SEQ ID NO: 469 is the determined cDNA sequence for clone 31855. SEQ ID NO: 470 is the determined cDNA sequence for clone 31858. SEQ ID NO: 471 is the determined cDNA sequence for clone 31861. 25 SEQ ID NO: 472 is the determined cDNA sequence for clone 31868. SEQ ID NO: 473 is the determined cDNA sequence for clone 31870. SEQ ID NO: 474 is the determined cDNA sequence for clone 31872. SEQ ID NO: 475 is the determined cDNA sequence for clone 31873. SEO ID NO: 476 is the determined cDNA sequence for clone 31877. 30 SEQ ID NO: 477 is the determined cDNA sequence for clone 31878.

SEQ ID NO: 478 is the determined cDNA sequence for clone 31885.

SEQ ID NO: 479 is the determined cDNA sequence for clone 31888.

SEQ ID NO: 480 is the determined cDNA sequence for clone 31890.

SEQ ID NO: 481 is the determined cDNA sequence for clone 31893.

SEQ ID NO: 482 is the determined cDNA sequence for clone 31898.

SEQ ID NO: 483 is the determined cDNA sequence for clone 31901.

SEQ ID NO: 484 is the determined cDNA sequence for clone 31909.

SEQ ID NO: 485 is the determined cDNA sequence for clone 31910.

SEQ ID NO: 486 is the determined cDNA sequence for clone 31914.

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DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy and diagnosis of cancer, such as colon cancer. The compositions described herein may include colon tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells). Polypeptides of the present invention generally comprise at least a portion (such as an immunogenic portion) of a colon tumor protein or a variant thereof. A "colon tumor protein" is a protein that is expressed in colon tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain colon tumor proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with colon cancer. Polynucleotides of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a sequence. Antibodies are generally immune system proteins, or antigen-binding fragments thereof, that are capable of binding to a polypeptide as described above. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B-cells that express a polypeptide as described above. T cells that may be employed within such compositions are generally T cells that are specific for a polypeptide as described above.

The present invention is based on the discovery of human colon tumor proteins. Sequences of polynucleotides encoding specific tumor proteins are provided in SEQ ID NO: 1-121, 123-197 and 205-486.

5 COLON TUMOR PROTEIN POLYNUCLEOTIDES

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Any polynucleotide that encodes a colon tumor protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides and more preferably at least 45 consecutive nucleotides, that encode a portion of a colon tumor protein. More preferably, a polynucleotide encodes an immunogenic portion of a colon tumor protein. Polynucleotides complementary to any such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes a colon tumor protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native colon tumor protein or a portion thereof.

Two polynucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and

compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

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Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 Methods in Enzymology vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) CABIOS 5:151-153; Myers, E.W. and Muller W. (1988) CABIOS 4:11-17; Robinson, E.D. (1971) Comb. Theor 11:105; Santou, N. Nes, M. (1987) Mol. Biol. Evol. 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) Proc. Natl. Acad., Sci. USA 80:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (i.e. gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of

hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native colon tumor protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

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It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Polynucleotides may be prepared using any of a variety of techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (i.e., expression that is at least two fold greater in a colon tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polypeptides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as colon tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (e.g., a colon tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide

probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

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For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with ³²P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by

amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., *PCR Methods Applic. 1*:111-19, 1991) and walking PCR (Parker et al., *Nucl. Acids Res. 19*:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

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In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

Certain nucleic acid sequences of cDNA molecules encoding portions of colon tumor proteins are provided in SEQ ID NO: 1-121, 123-197 and 205-486. These polynucleotides were isolated from colon tumor cDNA libraries using conventional and/or PCR-based subtraction techniques, as described below.

Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see Adelman et al., DNA 2:183, 1983). Alternatively, RNA molecules may be generated by in vitro or in vivo transcription of DNA sequences encoding a colon tumor protein, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated in vivo (e.g., by transfecting

antigen-presenting cells, such as dendritic cells, with a cDNA construct encoding a colon tumor polypeptide, and administering the transfected cells to the patient).

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A portion of a sequence complementary to a coding sequence (i.e., an antisense polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of a tumor protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (see Gee et al., In Huber and Carr, Molecular and Immunologic Approaches, Futura Publishing Co. (Mt. Kisco, NY; 1994)). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (e.g., promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

A portion of a coding sequence, or of a complementary sequence, may also be designed as a probe or primer to detect gene expression. Probes may be labeled with a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers, as noted above, are preferably 22-30 nucleotides in length.

Any polynucleotide may be further modified to increase stability in vivo. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In

general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

COLON TUMOR POLYPEPTIDES

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Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of a colon tumor protein or a variant thereof, as described herein. As noted above, a "colon tumor protein" is a protein that is expressed by colon tumor cells. Proteins that are colon tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with colon cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or

heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (i.e., specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a colon tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (e.g., 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

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Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, Fundamental Immunology, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (i.e., they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native colon tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (e.g., in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, 125 I-labeled Protein A.

As noted above, a composition may comprise a variant of a native colon tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native colon tumor protein in one or more substitutions, deletions, additions and/or insertions, such

that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

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Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity (determined as described above) to the identified polypeptides.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain non-conservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

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Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A

fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

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Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene 40*:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and

second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

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Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid

proteins containing the C-LYTA fragment at the amino terminus has been described (see Biotechnology 10:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

BINDING AGENTS

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The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a colon tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a colon tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a colon tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10³ L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as colon cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a colon tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies

this requirement, biological samples (e.g., blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

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Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example,

from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

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Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ⁹⁰Y, ¹²³I, ¹²⁵I, ¹³¹I, ¹⁸⁶Re, ¹⁸⁸Re, ²¹¹At, and ²¹²Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid.

Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

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Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

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T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a colon tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the ISOLEXTM system, available from

Nexell Therapeutics Inc., Irvine, CA. Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a colon tumor polypeptide, polynucleotide encoding a colon tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a colon tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

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T cells are considered to be specific for a colon tumor polypeptide if the T cells kill target cells coated with the polypeptide or expressing a gene encoding the T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., Cancer Res. 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a colon tumor polypeptide (100 ng/ml - 100 μg/ml, preferably 200 ng/ml - 25 μg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-γ) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a colon tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4+ and/or CD8+. Colon tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from either a patient or a related, or unrelated, donor and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4⁺ or CD8⁺ T cells that proliferate in response to a colon tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro*

or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a colon tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a colon tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a colon tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

PHARMACEUTICAL COMPOSITIONS AND VACCINES

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Within certain aspects, polypeptides, polynucleotides, T cells and/or binding agents disclosed herein may be incorporated into pharmaceutical compositions or immunogenic compositions (*i.e.*, vaccines). Pharmaceutical compositions comprise one or more such compounds and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds and an immunostimulant. An immunostimulant may be any substance that enhances or potentiates an immune response to an exogenous antigen. Examples of immunostimulants include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the compound is incorporated; *see e.g.*, Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition or vaccine.

A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the

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necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., Proc. Natl. Acad. Sci. USA 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner et al., Vaccine 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, Biotechniques 6:616-627, 1988; Rosenfeld et al., Science 252:431-434, 1991; Kolls et al., Proc. Natl. Acad. Sci. USA 91:215-219, 1994; Kass-Eisler et al., Proc. Natl. Acad. Sci. USA 90:11498-11502, 1993; Guzman et al., Circulation 88:2838-2848, 1993; and Guzman et al., Cir. Res. 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., Science 259:1745-1749, 1993 and reviewed by Cohen, Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and

5,075,109.

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Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide) and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of immunostimulants may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, Bortadella pertussis or Mycobacterium tuberculosis derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories. Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres: monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, TNFα, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, Ann. Rev. Immunol. 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT) (see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another preferred adjuvant is a saponin, preferably QS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the OS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

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The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule, sponge or gel (composed of polysaccharides, for example) that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical

compositions and vaccines to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

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Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency, and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see Zitvogel et al.*, *Nature Med. 4*:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcy receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide encoding a colon tumor protein (or portion or other variant thereof) such that the colon tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology* and cell Biology 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the colon tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be pulsed with a nonconjugated immunological partner, separately or in the presence of the polypeptide.

CANCER THERAPY

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In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as colon cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or

may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs.

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Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polypucleotides disclosed herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8+ cytotoxic T lymphocytes and CD4+ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive

polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., *Immunological Reviews 157*:177, 1997).

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Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions disclosed herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to nonvaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient.

but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a colon tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

METHODS FOR DETECTING CANCER

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In general, a cancer may be detected in a patient based on the presence of one or more colon tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum, urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as colon cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a colon tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of

the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length colon tumor proteins and portions thereof to which the binding agent binds, as described above.

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The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μg, and preferably about 100 ng to about 1 µg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

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In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20TM (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with colon cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20TM. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

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The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as colon cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered

positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

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In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use colon tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such colon tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a colon tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4⁺ and/or CD8⁺ T cells isolated from a patient is incubated with a colon tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated in vitro for 2-9 days (typically 4 days) at 37°C with one or more representative polypeptides (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of colon tumor polypeptide to serve as a control. For CD4⁺ T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8⁺ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

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As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a colon tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a colon tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the colon tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a colon tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a colon tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes will

hybridize to a polynucleotide encoding a polypeptide disclosed herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NO: 1-121, 123-197 and 205-486. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

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One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the disclosed compositions may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may

also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple colon tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

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DIAGNOSTIC KITS

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a colon tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a colon tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a colon tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a colon tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

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Example 1

ISOLATION AND CHARACTERIZATION OF COLON TUMOR POLYPEPTIDES BY PCR-BASED SUBTRACTION AND MICROARRAY ANALYSIS

A cDNA library was constructed in the PCR2.1 vector (Invitrogen, Carlsbad, CA) by subtracting a pool of three colon tumors with a pool of normal colon, spleen, brain, liver, kidney, lung, stomach and small intestine using PCR subtraction methodologies (Clontech, Palo Alto, CA). The subtraction was performed using a PCR-based protocol, which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were separately digested with five restriction enzymes that recognize six-nucleotide restriction sites (MluI, MscI, PvuII, SalI and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with Rsal according to the Clontech protocol. This modification did not affect the subtraction efficiency. Two tester populations were then created with different adapters, and the driver library remained without adapters.

The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs, and (d) unhybridized driver cDNAs. The two separate hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not

hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are over-expressed in colon tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

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To characterize the complexity and redundancy of the subtracted library, 96 clones were randomly picked and 65 were sequenced, as previously described. These sequences were further characterized by comparison with the most recent Genbank database (April, 1998) to determine their degree of novelty. No significant homologies were found to 21 of these clones, hereinafter referred to as 11092, 11093, 11096, 11098, 11103, 11174, 11108, 11112, 11115, 11117, 11118, 11134, 11151, 11154, 11158, 11168, 11172, 11175, 11184, 11185 and 11187. The determined cDNA sequences for these clones are provided in SEQ ID NO: 48, 49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101 and 109-111, respectively.

Two-thousand clones from the above mentioned cDNA subtraction library were randomly picked and submitted to a round of PCR amplification. Briefly, 0.5 µl of glycerol stock solution was added to 99.5 µl of pcr MIX (80 µl H₂0, 10 µl 10X PCR Buffer, 6 μl 25 mM MgCl₂, 1 μl 10 mM dNTPs, 1 μl 100 mM M13 forward primer (CACGACGTTGTAAAACGACGG), 1 μl 100 mM M13 reverse primer (CACAGGAAACAGCTATGACC)), and 0.5 µl 5 u/ml Taq polymerase (primers provided by (Operon Technologies, Alameda, CA). The PCR amplification was run for thirty cycles under the following conditions: 95°C for 5 min., 92°C for 30 sec., 57°C for 40 sec., 75°C for 2 min. and 75°C for 5 minutes.

mRNA expression levels for representative clones were determined using microarray technology (Synteni, Palo Alto, CA) in colon tumor tissues (n=25), normal colon tissues (n=6), kidney, lung, liver, brain, heart, esophagus, small intestine, stomach, pancreas, adrenal gland, salivary gland, resting PBMC, activated PBMC, bone marrow, dendritic cells, spinal cord, blood vessels, skeletal muscle, skin, breast and fetal tissues. The number of tissue samples tested in each case was one (n=1), except where specifically noted above; additionally, all the above-mentioned tissues were derived from humans. The PCR

amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, and fluorescent-labeled cDNA probes were generated by reverse transcription according to the protocol provided by Synteni. The microarrays were probed with the labeled cDNA probes, the slides scanned, and fluorescence intensity was measured. This intensity correlates with the hybridization intensity.

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One hundred and forty nine clones showed two or more fold over-expression in the colon tumor probe group as compared to the normal tissue probe group. These cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A and/or Model 377 (Foster City, CA). These sequences were compared to known sequences in the most recent GenBank database. No significant homologies to human gene sequences were found in forty nine of these clones, represented by the following sixteen cDNA consensus sequences: SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46 and 47, hereinafter referred to as Contig 2, 8, 13, 14, 20, 23, 29, 31, 35, 32, 36, 38, 41, 42, 50 and 51, respectively). Contig 29 (SEQ ID NO: 30) was found to be a Rat GSK-3-β-interacting protein Axil homolog. Also, Contigs 31 and 35 (SEQ ID NO: 32 and 33, respectively) were found to be a Mus musculus GOB-4 homolog. The determined cDNA sequences of SEQ ID NO: 1, 3-7, 9-14, 17-21, 23, 25-29, 31, 35, 37, 39, 42-45, 50, 51, 53, 55-58, 61-64, 70-78, 80-88, 91, 92, 94-98, 102-108 and 112 were found to show some homology to previously identified genes sequences.

Microarray analysis demonstrated Contig 2 (SEQ ID NO: 2) showed over-expression in 34% of colon tumors tested, as well as increased expression in normal pancreatic tissue, with no over-expression in normal colon tissues. Upon further analysis, Contigs 2, 8 and 23 were found to share homology to the known gene GW112. Contigs 4, 5, 9 and 52 showed homology to carcinoembryonic antigen (SEQ ID NO: 3, 4, 5 and 6, respectively). A representative sampling of these fragments showed over-expression in 85% of colon tumors, with over-expression in normal bone marrow and 3/6 normal colon tissues. Contig 6 (SEQ ID NO: 7), showing homology to the known gene sequence for villin, and was over-expressed in about half of all colon tumors tested, with a limited degree of low level over-expression in normal colon. Contig 12 (SEQ ID NO: 14), showing homology to Chromosome 17, clone hRPC.1171 I 10, also referred to as C798P, was over-expressed in

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approximately 70% of colon tumors tested, with low over-expression in 1/6 normal colon samples. Contig 14, also referred to as 14261 (SEQ ID NO: 16), showing no significant homology to any known gene, showed over-expression in 44% of colon tumors tested, with low level expression in half of normal colon tissues, as well as small intestine and pancreatic tissue. Contig 18 (SEQ ID NO: 21), showing homology to the known gene for L1-cadherin, showed over-expression in approximately half of colon tumors and low level over-expression in 3/6 normal colon tissues tested. Contig 22 (SEQ ID NO: 23), showing homology to Bumetanide-sensitive Na-K-Cl cotransporter was over-expressed in 70% of colon tumors and no over-expression in all normal tissues tested. Contig 25 (SEQ ID NO: 25), showing homology to macrophage inflammatory protein-3a, was over-expressed in over 40% of colon tumors and in activated PBMC. Contigs 26 and 48 (SEQ ID NOS: 25 and 26), showing homology to the sequence for laminin, was over-expressed in 48% of colon tumors and with low over-expression in stomach tissue. Contig 28 (SEQ ID NO: 29), showing homology to the known gene sequence for Chromosome 16 BAC clone CIT987SK-A-363E6, was overexpressed in 33% of colon tumors tested with normal stomach and 2/6 normal colon tissues showing low level over-expression. Contigs 29, 31 and 35 (SEQ ID NOS: 30, 32 and 33, respetively), also referred to as C751P, an unknown sequence showing limited and partial homology to Rat GSK-3\beta-interacting protein Axil homolog.and Mus musculus GOB-4 homolog, was over-expressed in 74% of colon tumors and no over-expression in all normal tissues tested. Contig 34 (SEQ ID NO: 35), showing homology to the known sequence for desmoglein 2, was over-expressed in 56% of colon tumors and showed low level overexpression in 1/6 normal colon tissues. Contig 36 (SEQ ID NO: 36), an unknown sequence also referred to as C793P, showed over-expression in 30% of colon tumor tissues tested. Contig 37 and 14287.2 (SEQ ID NOS: 37 and 116), an unknown sequence, but with limited (89%) homology to the known sequence for putative transmembrane protein was overexpressed in 70% of colon tumors, as well as in normal lung tissue and 3/6 normal colon tissues tested. Contig 38, also referred to as C796P and 14219 (SEQ ID NO: 38), showing no significant homology to any known gene, was over-expressed in 38% in colon tumors and no elevated over-expression in any normal tissues. Contig 41 (SEQ ID NO: 40), also referred to as C799P and 14308, an unknown sequence showing no significant homology to any known gene, was over-expressed in 22% of colon tumors. Contig 42, (SEQ ID NO: 41), also

referred to as C794P and 14309, an unknown sequence with no significant homology to any known gene, was over-expressed in 63% of colon tumors tested, as well as in 3/6 normal colon tissues. Contig 43 (SEQ ID NO: 42), showing homology to the known sequence for Chromosome 1 specific transcript KIAA0487 was over-expressed in 85% of colon tumors tested and in normal lung and 4/6 normal colon tissues. Contig 49 (SEQ ID NO: 45), showing homology to the known sequence for pump-1, was over-expressed in 44% of colon tumors and no over-expression in all normal tissues tested. Contig 50 (SEQ ID NO: 46), also referred to as C792P and 18323, showing no significant homology to any known gene, was over-expressed in 33% of colon tumors with no detectable over-expression in any normal tissues tested. Contig 51 (SEQ ID NO: 47), also referred to as C795P and 14317 was over-expressed in 11% of colon tumors.

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Additional microarray analysis yielded seven clones showing two or more fold overexpression in the colon tumor probe group as compared to the normal tissue probe group. Three of these clones demonstrated particularly good colon tumor specificity, and are represented by SEQ ID NO: 115, 116 and 120. Specifically, SEQ ID NO: 115, referred to as C791P or 14235, which shows homology to the known gene sequence for H. sapiens chromosome 21 derived BAC containing ets-2 gene, was over-expressed in 89% of colon tumors tested and in 5/6 normal colon tissues, as well as over-expressed at low levels in normal lung and activated PBMC. Microarray analysis for SEQ ID NO: 116 is discussed above. SEQ ID NO: 120, referred to as 14295, showing homology to the known gene sequence for secreted cement gland protein XAG-2 homolog, was over-expressed in 70% of colon tumors and in 5/6 normal colon tissues, as well as low level over-expression in normal small intestine, stomach and lung. All clones showing over-expression in colon tumor were sequenced and these sequences compared to the most recent Genbank database (February 12, 1999). Of the seven clones, three contained sequences that did not share significant homology to any known gene sequences, represented by SEQ ID NO: 116, 117 and 119. To the best of the inventors' knowledge, none of these sequences have been previously shown to be present in colon. The determined cDNA sequences of the remaining clones (SEQ ID NO: 113-115 and 120) were found to show some homology to previously identified genes.

Further analysis identified a clone which was recovered several times by PCR subtraction and by expression screening using a mouse anti-scid antiserum. The determined

full length cDNA sequence for this clone is provided in SEQ ID NO: 121, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 122. This clone is homologous with the known gene Beta IG-H3, as disclosed in U.S. Patent No. 5,444,164. Microarray analysis demonstrated this clone to be over-expressed in 75 to 80% of colon tumors tested (n=27), with no over-expression in normal colon samples (n=6), but with some low level over-expression in other normal tissues tested.

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Further analysis of the PCR-subtraction library described above led to the isolation of longer cDNA sequences for the clones of SEQ ID NO: 30, 115, 46, 118, 41, 47, 38, 113, 14 and 40 (known as C751P, C791P, C792P, C793P, C794P, C795P, C796P, C797P, C798P and C799P, respectively). These determined cDNA sequences are provided in SEQ ID NO: 123-132, respectively.

Using PCR subtraction methodology described above with minor modifications, transcripts from a pool of three moderately differentiated colon adenocarcinoma samples were subtracted with a set of transcripts from normal brain, pancreas, bone marrow, liver, heart, lung, stomach and small intestine. Modifications of the above protocol were included at the cDNA digestion steps and in the tester to drive hybridization ratios. In a first subtraction, the restriction enzymes PvuII, DraI, MscI and StuI were used to digest cDNAs, and the tester to driver ratio was 1:40, as suggested by Clontech. In a second subtraction, DraI, MscI and StuI were used for cDNA digestion and a tester to driver ratio of 1:76 was used. Following the PCR amplification steps, the cDNAs were clones into pCR2.1 plasmid vector. The determined cDNA sequences of 167 isolated clones are provided in SEQ ID NO: 205-371. These sequences were compared to sequences in the public databases as described above. The sequences of SEQ ID NO: 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369 and 371 were found to show some homology to previously identified ESTs. The remaining sequences were found to show some homology to previously identified genes.

Using the PCR subtraction technology described above, a cDNA library from a pool of primary colon tumors was subtracted with a cDNA library prepared from normal tissues, including brain, bone marrow, kidney, heart, lung, liver, pancreas, small intestine.

stomach and trachea. The determined cDNA sequences for 90 clones isolated in this subtraction are provided in SEQ ID NO: 372-461. Comparison of these sequences with those in the public databases as described above, revealed no homologies to the sequences of SEQ ID NO: 426, 445 and 453. The sequences of SEQ ID NO: 372-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455 and 457-461 showed some homology to previously identified genes, while the sequences of SEQ ID NO: 379, 405, 407, 408, 418, 424, 430-432, 437, 442, 444, 452 and 456 showed some homology to previously isolated ESTs.

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Example 2

USING SCID-PASSAGED TUMOR RNA

Human colon tumor antigens were obtained using SCID mouse passaged colon tumor RNA as follows. Human colon tumor was implanted in SCID mice and harvested, as described in Patent Application Serial No. 08/556,659 filed 11/13/95, U.S. Patent No. 5,986,170. First strand cDNA was synthesized from poly A+ RNA from three SCID mouse-passaged colon tumors using a Lambda ZAP Express cDNA synthesis kit (Stratagene). The reactions were pooled and digested with RNase A, T1 and H to cleave the RNA and then treated with NaOH to degrade the RNA. The resulting cDNA was annealed with biotinylated (Vector Labs, Inc., Burlingame, CA) cDNA from a normal resting PBMC plasmid library (constructed from Superscript plasmid System, Gibco BRL), and subtracted with streptavidin by phenol/chloroform extraction. Second strand cDNA was synthesized from the subtracted first strand cDNA and digested with S1 nuclease (Gibco BRL). The cDNA was blunted with Pfu polymerase and EcoRI adaptors (Stratagene) were ligated to the The cDNA was phosphorylated with T4 polynucleotide kinase, digested with restriction endonuclease XhoI, and size selected with Sephacryl S-400 (Sigma). Fractions were pooled, ligated to Lambda ZAP Express arms (Stratagene) and packaged with Gigapack Gold III extract (Stratagene). Random plaques were picked, phagemid was excised, transformed into XLOLR cells (Stratagene) and resulting plasmid DNA (Qiagen Inc., Valencia, CA) was sequenced as described above. The determined cDNA sequences for 17

clones isolated as described above are provided in SEQ ID NO: 133-151, wherein 133 and 134 represent partial sequences of a clone referred to as CoSub-3 and SEQ ID NO: 135 and 136 represent partial sequences of a clone referred to as CoSub-13. These sequences were compared with those in the public databases as described above. The sequences of SEQ ID NO: 139 and 149 showed no significant homologies to any previously identified sequences. The sequences of SEQ ID NO: 138, 140, 141, 142, 143, 148 and 149 showed some homology to previously isolated expressed sequence tags (ESTs). The sequences of SEQ ID NO: 133-137, 144-147, 150 and 151 showed some homology to previously isolated gene sequences.

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Example 3

USE OF MOUSE ANTISERA TO IDENTIFY DNA SEQUENCES ENCODING COLON TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encoding colon tumor antigens by screening of colon tumor cDNA libraries with mouse anti-tumor sera.

A cDNA expression library was prepared from SCID mouse-passaged human colon tumor poly A+ RNA using a Stratagene (La Jolla, CA) Lambda ZAP Express kit, following the manufacturer's instructions. Sera was obtained from the colon tumor-bearing SCID mouse. This serum was injected into normal mice to produce anti-colon tumor serum. Approximately 600,000 PFUs were screened from the unamplified library using this antiserum. Using a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (BRL Labs.), positive plaques were identified. Phage was purified and phagemid excised for several clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 46 of the isolated clones are provided in SEQ ID NO: 152-197. The predicted amino acid sequences for the cDNA sequences of SEQ ID NO: 187, 188, 189, 190, 194, 195 and 197 are provided in SEQ ID NO: 198-204, respectively. The determined cDNA sequences were compared with those in the public database as described above. The sequences of SEQ ID NO: 156, 168, 184, 189, 192 and 196 showed some homology to previously isolated ESTs. The sequences of SEQ ID NO: 152-

155, 157-167, 169-182, 183, 185-188, 190, 194, 195 and 197 showed some homology to previously identified genes.

Example 4

ISOLATION AND CHARACTERIZATION OF COLON TUMOR POLYPEPTIDES BY CONVENTIONAL SUBTRACTION

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Two cDNA libraries were constructed and used to create a subtracted cDNA library as follows.

Using the GibcoBRL Superscript Plasmid System with minor modifications, two cDNA libraries were created. The first library, referred to as CTCL, was prepared from a pool of mRNA samples from three colon adenocarcinoma tissue samples. Two of the samples were described as Duke's stage C and one as Duke's stage B. All three samples were grade III in histological status. A second library (referred to as DriverLibpcDNA3.1+) was prepared from a pool of normal tissues, namely liver, pancreas, skin, bone marrow, resting PBMC, stomach and brain. Both libraries were prepared using the manufacturer's instructions with the following modifications: an EcoRI-NotI 5' cDNA adapter was used instead of the provided reagent; the vector pCDNA3.1(+) (Invitrogen) was substituted for the pSPORT vector; and the ligated DNA molecules were transformed into ElectroMaxDH10B electrocompetent cells. Clones from the libraries were analyzed by restriction digest and sequencing to determine average insert size, quality of the library and complexity of the library. DNA was prepared from each library and digested.

The driver DNA was biotinylated and hybridized with the colon library tester DNA at a ratio of 10:1. After two rounds of hybridizations, streptavidin incubations and extractions, the remaining colon cDNAs were size-selected by column chromatography and cloned into the pCMV-Script vector from Stratagene. Clones from this subtracted library (referred to as CTCL-S1) were characterized as described above for the unsubtracted libraries.

The determined cDNA sequences for 18 clones isolated from the CTCL-S1 library are provided in SEQ ID NO: 462-479. Comparison of these sequences with those in the public databases, as described above, revealed no significant homologies to the sequences

of SEQ ID NO: 476, 477 and 479. The remaining sequences showed some homology to previously identified genes.

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In further studies, a cDNA library was prepared from a pool of mRNA from three metastatic colon adenocarcinomas derived from liver tissue samples. All samples were described as Duke's stage D. Conventional subtraction was performed as described above, using the DriverLibpcDNA3.1+ library described above as the driver. The resulting subtracted library (referred to as CMCL-S1) was characterized by isolating a set of clones for restriction analysis and sequencing.

The determined cDNA sequences for 7 clones isolated from the CMCL-S1 library are provided in SEQ ID NO: 480-486. Comparison of these sequences with those in the public databases revealed no significant homologies to the sequence of SEQ ID NO: 483. The sequences of SEQ ID NO: 480-482 and 484-486 were found to show some homology to previously identified genes.

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Example 5 SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

1. An isolated polypeptide comprising at least an immunogenic portion of a colon tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

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- (a) sequences recited in SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479 and 483;
- (b) sequences that hybridize to a sequence of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479 and 483 under moderately stringent conditions; and
- (c) a complement of a sequence of (a) or (b).
- 2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168,

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- 3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NO: 122 and 198-204.
- 4. An isolated polynucleotide encoding at least 15 amino acid residues of 10 a colon tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 15 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 20 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479 and 483 or a complement of any of the foregoing sequences.
- 5. An isolated polynucleotide encoding a colon tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303,

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- 6. An isolated polynucleotide comprising a sequence recited in any one of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479 and 483.
- 7. An isolated polynucleotide comprising a sequence that hybridizes to a sequence recited in any one of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479 and 483 under moderately stringent conditions.
 - 8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.

- 9. An expression vector comprising a polynucleotide according to any one of claims claim 4-8.
- 30 10. A host cell transformed or transfected with an expression vector according to claim 9.

- 11. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a colon tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479 and 483 or a complement of any of the foregoing polynucleotide sequences.
- 12. A fusion protein comprising at least one polypeptide according to claim 1.
 - 13. A fusion protein according to claim 12, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.

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- 14. A fusion protein according to claim 12, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.
- 15. A fusion protein according to claim 12, wherein the fusion protein comprises an affinity tag.
 - 16. An isolated polynucleotide encoding a fusion protein according to claim 12.
- 30 17. A pharmaceutical composition comprising a physiologically acceptable carrier and at least one component selected from the group consisting of:

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- (a) a polypeptide according to claim 1;
- (b) a polynucleotide according to claim 4;
- (c) an antibody according to claim 11;
- (d) a fusion protein according to claim 12; and
- (e) a polynucleotide according to claim 16.
- 18. A vaccine comprising an immunostimulant and at least one component selected from the group consisting of:
 - (a) a polypeptide according to claim 1;
 - (b) a polynucleotide according to claim 4;
 - (c) an antibody according to claim 11;
 - (d) a fusion protein according to claim 12; and
 - (e) a polynucleotide according to claim 16.
- 19. A vaccine according to claim 18, wherein the immunostimulant is an adjuvant.
 - 20. A vaccine according to any claim 18, wherein the immunostimulant induces a predominantly Type I response.

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- 21. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 17.
- 22. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a vaccine according to claim 20.
 - 23. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

24. A pharmaceutical composition according to claim 23, wherein the antigen presenting cell is a dendritic cell or a macrophage.

- 25. A vaccine comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with an immunostimulant.
 - 26. A vaccine according to claim 25, wherein the immunostimulant is an adjuvant.
- 10 27. A vaccine according to claim 25, wherein the immunostimulant induces a predominantly Type I response.
 - 28. A vaccine according to claim 25, wherein the antigen-presenting cell is a dendritic cell.

29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide encoded by a polynucleotide recited in any one of SEQ ID NO: 1-

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121, 123-197 and 205-486, and thereby inhibiting the development of a cancer in the patient.

30. A method according to claim 29, wherein the antigen-presenting cell is a dendritic cell.

- 31. A method according to any one of claims 21, 22 and 29, wherein the cancer is colon cancer.
 - 32. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a colon tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
 - (i) polynucleotides recited in any one of SEQ ID NO: 1-121, 123-

197 and 205-486; and

(ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the antigen from the sample.

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- 33. A method according to claim 32, wherein the biological sample is blood or a fraction thereof.
- 34. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 50.
- 35. A method for stimulating and/or expanding T cells specific for a colon tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:
 - (i) a polypeptide according to claim 1;
 - (ii) a polypeptide encoded by a polynucleotide comprising a sequence provided in any one of SEQ ID NO: 1-121, 123-197 and 205-486;
 - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); and
 - (iv) an antigen presenting cell that expresses a polypeptide of (i) or (ii),

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

- 36. An isolated T cell population, comprising T cells prepared according to the method of claim 35.
 - 37. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 36.

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38. A method for inhibiting the development of a cancer in a patient,

comprising the steps of:

- (a) incubating CD4⁺ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
 - (i) a polypeptide according to claim 1;
 - (ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NO: 1-121, 123-197 and 205-486;
 - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); and
 - (iv) an antigen-presenting cell that expresses a polypeptide of (i) or

10 (ii);

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such that T cells proliferate; and

- (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.
- 39. A method for inhibiting the development of a cancer in a patient, comprising the steps of:
 - (a) incubating CD4⁺ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
 - (i) a polypeptide according to claim 1;
 - (ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NO: 1-121, 123-197 and 205-486;
 - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); and
 - (iii) an antigen-presenting cell that expresses a polypeptide of (i) or

25 (ii);

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such that T cells proliferate;

- (b) cloning at least one proliferated cell to provide cloned T cells; and
- (c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.
 - 40. A method for determining the presence or absence of a cancer in a

patient, comprising the steps of:

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- (a) contacting a biological sample obtained from a patient with a binding agent that binds to a colon tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NO: 1-121, 123-197 and 205-486; and
 - (ii) complements of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
- 41. A method according to claim 40, wherein the binding agent is an antibody.
- 42. A method according to claim 43, wherein the antibody is a monoclonal antibody.
 - 43. A method according to claim 40, wherein the cancer is colon cancer.
- 44. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a colon tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-121, 123-197 and 205-486 or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

- (d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 45. A method according to claim 44, wherein the binding agent is an antibody.
 - 46. A method according to claim 45, wherein the antibody is a monoclonal antibody.
 - 47. A method according to claim 44, wherein the cancer is a colon cancer.

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- 48. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a colon tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-121, 123-197 and 205-486 or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
 - (c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
- 49. A method according to claim 48, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
 - 50. A method according to claim 48, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
 - 51. A method for monitoring the progression of a cancer in a patient,

comprising the steps of:

- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a colon tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-121, 123-197 and 205-486 or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
 - (d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 15 52. A method according to claim 51, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
 - 53. A method according to claim 51, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

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- 54. A diagnostic kit, comprising:
- (a) one or more antibodies according to claim 11; and
- (b) a detection reagent comprising a reporter group.
- 25 55. A kit according to claim 54, wherein the antibodies are immobilized on a solid support.
 - 56. A kit according to claim 54, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.
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57. A kit according to claim 54, wherein the reporter group is selected

from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

58. An oligonucleotide comprising 10 to 40 contiguous nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a colon tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479 and 483 or a complement of any of the foregoing polynucleotides.

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59. A oligonucleotide according to claim 58, wherein the oligonucleotide comprises 10-40 contiguous nucleotides recited in any one of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479 and 483.

- 60. A diagnostic kit, comprising:
- (a) an oligonucleotide according to claim 59; and
- (b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.

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SEQUENCE LISTING

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caaaagcaca gaagcacatc acatacacca gcaaggtttc caactactgc actgattaac 180 tagatactct caatagcttt tctatagctc gtcctagaaa aaaaaattaa attttcattt 240 tcttacaagt tccaggctta aacaaaggca aaaattacat gcaacaactg atacactcat 300 aagttgcaca tatgctccaa ggtctttatt agataacaat aaatgctagc actttgtcac 360 tgccatcaga ttttccttat agtcttagag tcatgtaaat aaaagttcca taatgaaatt 420 aaagaaaatt aattttcta atcttagatc agttccatag aaaactatta attttttaa 480	tatagactag gacttqaaca tcaaaqqaaa	aatagacaaa	gactagatga	tasagtcatt	
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<213> Homo sapien

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caaatggtat gtttttcagt acagttggat gtcgtcctac aagatgtggt gaatttgaaa
                                                                       180
agaataaccc tgatctttac ttaaaggagt tgctaaatct tgctgaaaac aataaaggga
                                                                       240
aagttgtggc aataggagaa tgcggacttg attttgaccc gactgcagtt ttgtcccaaa
                                                                       300
gatactcaac tcaaatattt tgaaaaacag tttgaactgt cagaacaaac aaaattacca
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      <211> 407
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                                                                       120
cagagcactc cctaatttat gtgctatata aatatgtcag atgtacatag agatctattt
                                                                       180
tttctaaaac attcccctyc ccactcctct cccacagagt gctggactgt tccaggccct
                                                                       240
ccagtgggct gatgctggga cccttaggat ggggctccca gctcctttct cctgtgaatg
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gaggcagaag acctccaata aagtgccttc tgggcttttt ctaacctttg tcttagctac
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ctgtgtactg aaatttgggc ctttggatcg aatatggtca agaggtt
                                                                       407
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gtattaaagc agcggcagcc gctgcacgca gacatgaggg ctaggttaaa acagtaagat
                                                                       120
caagttgttt ggacagaaag gctacagagt gtggtcctgg ctcttgtgta agaattacga
                                                                       180
ccacgctaac catgcctagg aaggaaagga gttattgttt tgtagaaagg tgctggggtt
                                                                       240
tgagagatca gtcggacacg attggcaggg agagcacgtg tgtttttatg agaattatgc
                                                                       300
ccgagatagg taacagatga ggaagaaatt tgggcttgat tgaagtaatg ggggctgtct
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gtgaagcttt gcagcagtac agcctaggta atttgctgag cctaa
                                                                       405
      <210> 19
      <211> 401
      <212> DNA
      <213> Homo sapien
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                                                                      120
gctgcttcaa gcgggattag gggcggcgtg ggagcctaga gtgggagaga ttaagctgaa
                                                                      180
gggaggtctt gtggtaaggg gtgatatcat ggggatgtta gaagaaacat ttgtcgtata
                                                                      240
gaatgattgg tgatggcctg gatacggttt tggatgattt gagaagctaa atggaagata
                                                                      300
caaggtccga ataaaaggag gagaaaaatg ggtattaaat gtctaagaat tgggaggacc
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                                                                     120
tegatgatet tgaagtaatg getecagtet etgacetggg gteeettett etceaagtge
                                                                     180
teceggattt tgetetecag ceteeggtte teggteteca ggeteeteac tetgtecagg
                                                                     240
taagaggcca ggcggtcgtt caggctttgc atggtctcct tctcgttctg gatgcctccc
                                                                     300
attectgeca gacceegge tateceggtg q
                                                                     331
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                                                                     120
agcttatgtc cagaccttct ggatccttgg cagtcacatt gcccacttta gtgcctatag
                                                                     180
ctacatcctc actgactttc gcttggaata cgtgttggga aaattgaggt gcttcattca
                                                                     240
catctgtcac aataagncgt gaacttggca aaagaacttg cattgtactt cacaccaaac
                                                                     300
actagaggct caggattttc tgctttgaac acaatgttgg aaacag
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gggactgggc gctaccaggt gcttcttaat gaagaggata actcagaatc atcggctata
                                                                     120
gagcagccac ctacttcaaa cccagcaccc gcagattgtg caggctgcgt cttcagcacc
                                                                     180
agcacttgaa actgactctt cccctccacc atatagtagt attactggtg gaagtaccta
                                                                     240
caacttcaga tacagaagtt tacggtgagt tttatcccgt gccacctccc tatagcgttg
                                                                     300
ctacctctct tcctacnwta cgatgaaagc tgagaaggct aaagctgctg caatggcatg
                                                                     360
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     <211> 251
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agaaagtact ccaaccagag atgctgtggt cacgtatact gcagaaagta aaggagtcgt
                                                                     120
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gaagtttggc tggatcaagg gtgtattagt acgttgtatg ttaaacattt ggggtgtgat
                                                                       180
gcttttcatt agattgtcat ggattgtggg tcaagctgga ataggtctat caqtccttqt
                                                                       240
aataatgatg g
                                                                       251
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cagetecage egeagettar geagegggag gttetgtgte ceagttgttt tecaatttea
                                                                       120
ccggctcccg tggatgamcg ygggacctgy caswgctcct gtktycctgc yagsacacca
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cnytttyccg tggacacrar kggaacckct tggaattcac agctyatgtt ctttctcara
                                                                       240
agttttgagaa agaactttct aaagtgaggg aatatgtcca attaattagt qtqtatqaaa
                                                                       300
agaaactgtt aaacctaact gtccgaattg acatcatgga raaaggatac catttcttac
                                                                       360
actgaactgg acttcgagct gatcaaggta gaagtgaagg agatggaaaa actggtcata
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С
                                                                       421
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gcaattacaa caatttagga nacaaaacaa tataaacaaa agaatgttaa atagttttt
                                                                       120
ttaaaaaaata gcttgttgct tgcaanaaag tccatataat cttattcccc cccaaatata
                                                                       180
attitatact tigcactaaa ccaaaatagc tiatggaaaa tiagtattaa atagctaaac
                                                                       240
acagaaaacc tacagctata aataacataa aatacagttt aactttaatg ngatgcttaa
                                                                       300
acaaagcaaa ctatgatgca atatgaatca acttcattaa ttggacaagt ccagnggagg
                                                                       360
cacaaattag ataagcacta a
                                                                       381
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      <211> 401
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actgggatag totggotoco caaaaaaggg tggagagtta ggttgaatgt cagogootg ataatcaggo tttoccagag agtotgogta tggattgatt otaaaacttg tatgttoca attotttotg gatootggat ggttoaaatt ggototgggt o	g 300 g 360 401
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<pre><210> 32 <211> 401 <212> DNA <213> Homo sapien</pre>	297
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	ggatgagacg ttgagccctg				ggcaaagtgg	360 401
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	tgagaccaaa					240
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	ggatcccacc				tagcttgaat	360
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	> 401 > DNA					
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	> 401					
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	ttttacegetge ttttacatta			-		120
	gaacagttgt					180
	ggtttttgtg					240
	tgtatatagt					300 360
	: agtacagtac : aagctttccc				cogococaca	401
	_	_ _				
)> 37 L> 401					
	2> DNA					
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antaagcatg ganchtgatc ntttnctnng cactccttta cgacacggaa acangnatca
                                                                       120
ncatgatggt accaganace ttatcacena egegeaenga netgaetnat tecaaaqaqt
                                                                       180
tgnggttacg gncatccggt cattgctcgt gcccattgct gcagggctga tnctactggt
                                                                       240
gettattatg ntggeectga ggatgeteca caatgaatat aageatgetg catgateage
                                                                       300
ggcaacanat gctctgccgt ttgcactaca tctttcacgg acacnatntc gaanacgggc
                                                                       360
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                                                                       401
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                                                                       120
agteetttag ataaaaggee aggagtegta ceaacataga taccaaatee aggagaacae
                                                                       180
agaccagega taagagggac getteeceat gacceagace ageetaaage eeetgtgggg
                                                                       240
gcagccagtg gggagctgtc agaccttgga catggtggtc tttgagaatg ggtctgccct
                                                                       300
tctctccctg accagttggg atagacacct gactggaatc cttgacactg gcaggtgttt
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      <223> n = A,T,C or G
      <400> 39
tctggtangg agcaattcta ttatttggca ttgcatggct gggttgaatt aaaacaggga
                                                                       60
gtgagaacag gtgagtctag aagtccaact ctgaaaagga ccactgtaca tttgaacaca
                                                                       120
cggctgtgtt aaagatgctg ctaatgtcag tcactgggtg cactaaagga tctcttattt
                                                                      180
tatgtaaaac gttgggaatg acaagatana actgatactc tggtaagtta ccctctgaag
                                                                      240
ctacttcttg tgaaatacta atgacagcat catcctgcca agcgaaagag gcaggcataa
                                                                      300
gcaaggacaa attaaaaggg ggtaagagcc ttatcatgat gaggagtctt gttttgacat
                                                                      360
cttgggaaaa gctgtccata gtgtgaagtc gtcaatttct c
                                                                      401
      <210> 40
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 40
tctggtcacc caactcttgt ggaagaggg aattgagatc gagtactgaa tatctggcag
                                                                       60
agaggctgga atccttcagc cccagagccc agggaccact ccagtagatg cagagaggg
                                                                      120
```

```
cctgcccagg ggtcagggca gtgggtatca ctggtgacat caagaatatc agggctgggg
                                                                        180
aggeatettt gttteetggt geeeteetea aagttgetga caetttgggg aegggaaggg
                                                                        240
gtagaagtag ggctgctcct tttggagctg gagggaatag acctggagac agagttgagg
                                                                        300
cagtcgggct gtccaggttc taagcatcac agcttctgca ctgggctctg aggagattct
                                                                        360
cagccagagg atcccagcct cctcctccct caaatgtcaa g
                                                                        401
      <210> 41
      <211> 401
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(401)
      \langle 223 \rangle n = A,T,C or G
      <400> 41
ctggactaaa aatgtccact atggggtgca ctctacagtt tttgaaatgc taggaggcag
                                                                        60
aaggggcaga gagtaaaaaa catgacctgg tagaaggaag agaggcaaag gaaactaggt
                                                                        120
ggggaggatc aattagagag gaggcacctg ggatccacct tcttccttan gtcccctcct
                                                                       180
ccatcagcaa aggagcactt ctctaatcat gccctcccga agactggctg ggagaaggtt
                                                                       240
taaaaacaaa aaatccagga gtaagagcct taggtcagtt tgaaattgga gacaaactgt
                                                                       300
ctggcaaagg gtgcganagg gagcttgtgc tcangagtcc agcccgtcca gcctcggggt
                                                                       360
gtangtttct gaagtgtgcc attggggcct caccttctct g
                                                                       401
      <210> 42
      <211> 310
      <212> DNA
      <213> Homo sapien
      <400> 42
ggttcgacaa atccccaaaa atggcaaatt aagccctgtg acaaaataag ttattggatc
                                                                        60
atacagaaat agcccaaatc tggaaatttt gaattaaaat tgtaatcctg taaaacaagt
                                                                       120
tttggggtga atggatttct ttaataccaa taatattttt aattcccacc acagatggat
                                                                       180
ttgctgaata tgctaatgct gtgaatgaga aaacaatttt ggggtaggta tacccacaag
                                                                       240
taatctgatg acaaaataaa ccacagactg atgtcaaatg gacaaaaaac tgaaaatatg
                                                                       300
ctgtgagaaa
                                                                       310
      <210> 43
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 43
aggtcactta cacttgtgac cagtgtgggg cagagaccta ccagccgatc cagtctccca
                                                                        60
ctttcatgcc tctgatcatg tgcccaagcc aggagtgcca aaccaaccgc tcaggagggc
                                                                       120
ggctgtatct gcagacacgg ggctccagat tcatcaaatt ccaggagatg aagatgcaag
                                                                       180
aacatagtga tcaggtgcct gtgggaaata tccctcgtag tatcacggtg ctggtagaag
                                                                       240
gagagaacac aaggattgcc cagcctggag accacgtcag cgtcactggt attttcttgc
                                                                       300
caatcctgcg cactgggttc cgacaggtgg tacagggttt actctcagaa acctacctgg
                                                                       360
aagcccatcg gattgtgaag atgaacaaga gtgaggatga t
                                                                       401
      <210> 44
```

<211> 401

<212> DNA

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<213> Homo sapien

<400> 47

```
<400> 44
atccctqtaa qtctattaaa tgtaaataat acatacttta caacttctct taqtcqqccc
                                                                        60
ttqqcaqatt aaatctttgc aaaattccat atgtgctatt gaaaaatgaa ataaaacctc
                                                                       120
agatgtctga attcttattt caaatacagt tatataatta ttttaaatta caatatacaa
                                                                       180
tttctgttaa atacaactgt taagggattc tgagaacaat tataagatta taataatata
                                                                       240
tacaaactaa cttctgaaat gacatgggtt gtttccttcc caccctccta ccctctcaaa
                                                                       300
gagtttttqc atttgctgtt cctgqttqca aaaggcaaaa qaaaatctaa aaataqtctq
                                                                       360
                                                                       401
tgtgtgtcca cgacatgctc gctcctttga gaatctcaaa c
      <210> 45
      <211> 401
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(401)
      <223> n = A, T, C or G
      <400> 45
gtgcctgctg cctggcagcc tggccctgcc gctgcctcag gaggcgggag gcatgagtga
                                                                        60
gctacagtgg gaacaggctc aggactatct caagagattt tatctctatg actcagaaac
                                                                       120
aaaaaatgcc aacagtttag aagccaaact caaggagatg caaaaaattc tttggcctac
                                                                       180
ctatactgga atggtaaact cccgcgtcat anaaataatg caanaagccc agatgtggag
                                                                       240
tgccagatgt tgcagaatac tcactatttc caaatagccc aaaatggact tccaaagtgg
                                                                       300
tcacctacag gatcgtatca tatactcgag acttaccgca tattacagtg gatcgattag
                                                                       360
tgtcaaaggc tttaaacatg tggggcaaag agatcccct g
                                                                       401
      <210> 46
      <211> 401
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(401)
      <223> n = A,T,C or G
      <400> 46
gtcagaattg tctttctgaa aggaagcact cggaatcctt ccgaactttc caagtccatc
                                                                        60
catgattcan agatactgcc ttctctctct ctgggatttt atgtgtttct gatagtgaat
                                                                       120
tgttgatgta tttgctactt tgcttctttt ctctttcaag acttgatcat tttatatgct
                                                                       180
gnttggagaa aaaaagaact tttggtagca aggaggtttc aagaaatgat tttggatttt
                                                                       240
ctgctgcgga atttctcggc acctacctgt agtatggggc acttggtttg gttgcagagt
                                                                       300
aagaaggtgg aagaatgagc tgtacttggt taagcagttg aaaccttttt tgagcaggat
                                                                       360
ctgtaaaagc ataattgaat ttgtttcacc cccgtggatt c
                                                                       401
      <210> 47
      <211> 401
      <212> DNA
      <213> Homo sapien
```

```
ggtctgcagc aatgcacttc aaccatacat actgcttcca ctagctaata ccaaatgcag
                                                                        60
gttctcagat ccagacaaat ggaggaaaag aacatttatg cttccgtttc agaaagccaa
                                                                       120
                                                                       180
qtcqtaqttt tqqcccttcc tttctctaaa gtttattccc aaaaacaggt agcattcctg
attgggcaga gaagaggata ttttcagccc acatctgctg caggtatgtc attttctccc
                                                                       240
atcttcactg tgactagtaa agatctcacc acttctcttt ggaatttcca actttgcttg
                                                                       300
tgattgaatg tcacttcgtg aatttgtatt atgtcagatc acttggcatt gctcttccat
                                                                       360
atgcatcaag ttgccaggca ctaaacccaa tgttcatgaa c
                                                                       401
      <210> 48
      <211> 430
      <212> DNA
      <213> Homo sapien
      <400> 48
                                                                        60
acataacttg taaacttttt ctgcttgggg gctgtaacag acagaagagt aaagactaca
aggattttct gaagatgctt caatgaaaat catcatttcc tctttagtca tcccaagtct
                                                                       120
tggtttgaaa aacttgggca tggacttata cagaccttga accaccactg acttatcatt
                                                                       180
gggtggcaga ccttgaaacc aagctctctg tgttacttct gaaagtgcat caattctgat
                                                                       240
ttggctaaga acagaagaca aatactggga tcgtgattct gtgttatact ctagccacag
                                                                       300
                                                                       360
catagoaget tetegaacgg tttetteett ttetacattt aaattgteac taetgagaat
atctatcagt aggtcatgtg acagacctgc cccggggccg gcccgctcga tgcttgccga
                                                                       420
                                                                        430
atatcatggt
      <210> 49
      <211> 57
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(57)
      <223> n = A,T,C or G
      <400> 49
ggtattaaca atatcangca ctcattcttc ccctcttatg aaanggatna attttta
                                                                        57
      <210> 50
      <211> 327
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(327)
       <223> n = A, T, C \text{ or } G
       <400> 50
gatggnggtn tccacaagan tnaangtncn tattaantan nncttgtaga nccacttnna
                                                                         60
ttaattgnnn tatgnntgnc cttctggtgg ntgtngaagc ttcatatnnt ntttggacat
                                                                        120
 cattacacgt cttagctctt tnaagnacaa ctttaatgct atatgaattt tgccattttn
                                                                        180
 gctaacactg gtatgctccn ngcatccacc atnccacntg gaattattta ttncnttcat
                                                                        240
 attaatnttt tgtttaccaa atctnacttg acccgaacga aactttctgn gtattttang
                                                                        300
                                                                        327
 gccccnccat tcttactttt caagcct
```

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<211> 236
      <212> DNA
      <213> Homo sapien
      <400> 51
cgtctcgaag aagcgctgca ggccgatgat ggactgcacg tctgccttgt cctcagttaa
                                                                        60
cttgttgaat tgcttgaaca tgcggcccac atcctgggca aactcctgtg gggagctgta
                                                                       120
gggaggtgac aacttctcct ggaggcgggc acggatcagg gtcagatcca gggtgccacc
                                                                       180
gggctggtcc agggagaagg tggagtcgta gccagacctg cccgggcggc cgctcg
                                                                       236
      <210> 52
      <211> 291
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(291)
      <223> n = A,T,C or G
      <400> 52
ctcacatcct gggtccggct gtagagctgc accatggtgc tgagcgcccc ctccagctcc
                                                                        60
                                                                       120
ttgtagatgt aaaggacggc gaaggagctg tagtctgtgt ccacgatgcg cacgtccagg
tagcccaagg cogggactot gaagttgtoo otoggagooc accttcangt actogggcat
                                                                       180
ccacctggtt acagcentic gneeteggna actecaintg gaetttacag geogecetee
                                                                       240
tetgtgggcc tgatggneet tgeaggacat nggaacaegg gagetenett t
                                                                       291
      <210> 53
      <211> 95
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(95)
      <223> n = A, T, C or G
      <400> 53
gtctgtgcag tttctgacac ttgttgttga acatggntaa atacaatggg tatcgctgan
                                                                        60
cactaagttg tanaanttaa caaatgtgct gnttg
                                                                        95
      <210> 54
      <211> 66
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(66)
      <223> n = A, T, C \text{ or } G
      <400> 54
cctnaatnat ntnaatggta tcaatnnccc tgaangangg gancggngga agccggnttt
                                                                        60
gtccgg
                                                                        66
```

```
<210> 55
      <211> 265
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(265)
      \langle 223 \rangle n = A,T,C or G
      <400> 55
atctttcttc tcagtgcctt ggccntgttg agtctatctg gtaacactgg agctgactcc
                                                                         60
ctgggaagag aggccaaatg ttacaatgaa cttaatggat gcaccaagat atatgaccct
                                                                        120
gtctgtggga ctgatggaaa tacttatccc aatgaatgcc gtgttatgtt tttgaaaatc
                                                                        180
ggaaacgcca gacttctatc ctcattcaaa aatctgggcc ttnctgaaaa ccaqqqtttt
                                                                        240
naaaatccca ttcnggtcnc cggcg
                                                                        265
      <210> 56
      <211> 420
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(420)
      \langle 223 \rangle n = A,T,C or G
      <400> 56
gagcggccgc ccgggcaggt cctcgcggtg acctgatggg atttcaaaac cttggttctc
                                                                        60
agcaaggccc agatttttga atgangatag aagtctggcg tttccgattt tcaaaacata
                                                                        120
acacgcattc attgggataa gtatttccat cagtcccaca gacngggtca tatatcttgg
                                                                        180
gtgcatccat taagttentt tgttaacatt tgggeetete ttteecangg gaatteaget
                                                                        240
cccagttgtt taccaanatt naactccacc ggggccaaag gcncttgaaa aaaaaaanaa
                                                                        300
ttccttgttt accttccttg ggcttnaagt tctggcgtcc aaaagttcaa tttgaaaact
                                                                        360
gcaccgcact taccacgtct cttcnagaan cctggggaca cctcggccgc gaccacgcta
                                                                        420
      <210> 57
      <211> 170
      <212> DNA
      <213> Homo sapien
      <400> 57
gaagcggagt tgcagcgcct ggtggccgcc gagcagcaga aggcgcagtt tactgcacag
                                                                        60
gtgcatcact tcatggagtt atgttgggat aaatgtgtgg agaagccagg gaatcgccta
                                                                        120
gactetegea etgaaaattg teteteeaga eeteggeege gaceaegeta
                                                                        170
      <210> 58
      <211> 193
      <212> DNA
      <213> Homo sapien
      <400> 58
attttcagtg cgagagtcta ggcgattccc tggcttctcc acacatttat cccaacataa
                                                                        60
ctccatgaag tgatgcacct gtgcagtaaa ctgcgccttc tgctgctcgg cggccaccag
                                                                       120
gcgctgcaac tccgcttcat cggcttcgcc cagctccgcc attgttcgcc acctgcccgg
                                                                       180
```

```
193
gcggccgctc gaa
     <210> 59
     <211> 229
     <212> DNA
     <213> Homo sapien
     <400> 59
cgcaactctc gagcatttat atacaatagc aaatcatcca gtgtgttgta cagtctataa
                                                                     60
                                                                     120
tactocaaca gtotoccato tgtattoaat ggogocacco aatacagtoo tttgtttgga
tgctggggag agtaatccct accccaagca ccatatagat aagaaaaccc tctccagttg
                                                                     180
agetgaacca cagaeggttt getgatacct geeegggegg eegetegaa
                                                                     229
    . <210> 60
     <211> 340
     <212> DNA
     <213> Homo sapien
     <400> 50
tegageggee geeegggeag gteetetaaa gateaaaaca eeeetgtegt eeaceeteet
                                                                     .60
cccastccag ggaagetgtg gteatggtgg tgtggtgaac atcagcaaac cgtctgtggt
                                                                     120
tcagetcaac tggagagggt tttettatet atatggtget tgggggtaggg attactetee
                                                                     180
ccagcatcca aacaaaggac tgtattgggt ggcgccattg aatacagatg ggaaactgtt
                                                                     240
ggagtattat aaactggtac aacacactgg atgatttgct attgtatata aatgctcgag
                                                                     300
aattgeggat cacctatgga ceteggeege gaccaegetg
                                                                     340
      <210> 61
      <211> 179
      <212> DNA
      <213> Homo sapien
     <220>
      <221> misc_feature
      <222> (1)...(179)
      <223> n = A, T, C or G
      <400> 61
tttttgtgac ggacgnttgg agtacatgtc ccaggatcac atccagcagc tagagtggct
                                                                      60
gggacaaget ggeggnggee aageactgtt gaaacnatag gggtetgggn gnactegggt
                                                                     120
tnaagtggtt ggtccgantn ttnataacct tgtcngaacc nancatctcg gttgncang
                                                                     179
      <210> 62
      <211> 78
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(78)
      <223> n = A,T,C or G
      <400> 62
agggcgttcg taacgggaat gccgaagcgt gqqaaaaaqg gagcggtggc nggaagacqq
                                                                      60
ggatgagctt angacaga
                                                                      78
```

```
<210> 63
      <211> 410
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(410)
      \langle 223 \rangle n = A,T,C or G
      <400> 63
cccagttact tggggaggct gaggcaggga gaatcctttg aacccggngg gtgggaggtt
                                                                    60
gcagtgagcc cgagatagca ccattgcact tccancatgg ggtggacaga gtgagactct
                                                                    120
180
tntcccattt caagteetga aaatagagga teagaaatgt tgaggaatte tttaggatag
                                                                    240
aaagggagat gggattttac ttatggggaa agaccgcaaa taaagactgn aacttaacca
                                                                    300
cattccccaa gtgnaaggtg ttacccaaga agtaggaacc cttttggctn ttaccttacc
                                                                    360
ttccngaaaa aaacttattn cttaaaatgg aaacccttaa agcccgggca
                                                                    410
      <210> 64
      <211> 199
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(199)
      <223> n = A,T,C or G
      <400> 64
cttgttctca aaaaggtcaa agggagcccg acgaggaata aatagcaatg ccctgaattc
                                                                    60
caactgacct tctacagaaa agtgcttgac tgccaagtgg tcttcccagt cattagtgag
                                                                   120
gctcttgtag aattctccat actcctcttg ggngangnca tnagggtttn nggcccaaat
                                                                   180
aggntgggcc tngttaagt
                                                                   199
      <210> 65
      <211> 125
      <212> DNA
      <213> Homo sapien
     <220>
      <221> misc_feature
     <222> (1)...(125)
     <223> n = A,T,C or G
     <400> 65
agcggtacag ttctgtcctg gcatcatcat tcattgtagt atggtcaata ggtgccatga
                                                                    60
aactcagtag cttgctaagg acatgaaacc gaagtttcct gcctttgctg gcctngtngn
                                                                   120
gggta
                                                                   125
     <210> 66
     <211> 204
     <212> DNA
     <213> Homo sapien
```

```
<400> 66
attcagaatt ctggcatcgg tatttctata aagtccatca gttagagcag gagcaggccc
                                                                        60
ggagggacgc cctgaagcag cgggcggaac agagcatctc tgaagagccc ggctgqqaqq
                                                                       120
aggaggaaga ggagctcatg ggcatttcac ccatatctcc aaaagaggca aaggttcctg
                                                                       180
tggacctcgg ccgcgaccac gcta
                                                                       204
      <210> 67
      <211> 383
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (383)
      <223> n = A,T,C or G
      <400> 67
tcagggcctc caggcagcca gttttgcagg anattcagca cctagngtct tcctgcctna
                                                                       60
cgctcccaag aacctgctcc tgcaggggga acatcagaac tcgtccttga tgtcaaaatg
                                                                       120
gggctggtct tnaggcttga agtccaggtt agggctgcca tcctcattga gaattctccq
                                                                       180
ggcagtgtan ccgacgatgg ggtatttggc tttgtacact ttqqtqaaaa cctnatccaq
                                                                       240
ggcctccagt tccttggccg tganacccgt antgtcatgg gtgaggtctg caggatccaa
                                                                       300
ggaCatcttg gctacccctc tagtggagtc cttccccgtc aaggcattgt aaggqqctcc
                                                                       360
tcgtccataa aactcctttt cgg
                                                                       383
      <210> 68
      <211> 99
      <212> DNA
      <213> Homo sapien
      <400> 68
tcacatctcc ttttttttt aactttttca aatttttgtg ttaaatagaa ggctaaaggg
                                                                        60
ttagatttaa gtttctgcta cattgaccct atttaccta
                                                                        99
      <210> 69
      <211> 37
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(37)
      <223> n = A,T,C or G
      <400> 69
gagaaggacn tacggncctg ntantanang aatctcc
                                                                        37
      <210> 70
      <211> 222
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(222)
```

```
<223> n = A,T,C \text{ or } G
      <400> 70
gtgggtcatt tttgctgtca ccagcaacgt tgccacgacg aacatccttg acagacacat
                                                                         60
tettgacatt gaageecaca ttgteeccag gaagagette acteaaaget teatggegea
                                                                        120
tttcgacaga ttttacttcc gttgtaacgt tgactggagc aaaggtgacc accataccgg
                                                                        180
gtttgagaac acccantcac ctgccccggg cggccgctcg aa
                                                                        222
      <210> 71
      <211> 428
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(428)
      <223> n = A,T,C or G
      <400> 71
caggagtatt ttgtagaaaa gccagaagag cattagtaga tgtatggaaa tatacggtag
                                                                         60
ggcacacgct gacagtactt ttcccaagcc acgccgtatt tcttcttaca gtqqtactcg
                                                                        120
tcacgagctt ctcggtggac aagcaacatg gtgaaataaa ttatgtagaa ataaggcaga
                                                                        180
atgtggttaa aaccacatgg gagggaccac gccaaggcca tgatgagatc acccaagtaa
                                                                        240
ttggggtggc gaacaaagcc ccaccatcca gaaactagaa naatttttcc cgttgaaata
                                                                        300
tgaatggntt ttaaatgtgc aagctttgga tcactgggaa ttttcccgaa tgccttttc
                                                                        360
tganaattgc accttnggaa gantccttac cccaagnttc agaccattat ttnaaaagcn
                                                                       420
ttggaact
                                                                        428
      <210> 72
      <211> 264
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(264)
      \langle 223 \rangle n = A,T,C or G
      <400> 72
gaataaagag cttactggaa tccagcaggg ttttctgccc aaggatttgc aagctgaagc
                                                                        60
tctctgcaaa cttgatagga gagtaaaaag ccacaataga gcagtttatg aagatcttgg
                                                                       120
aggagattga cacacttgat cctgccagaa aatttcaaag acagtagatt gaaaaggaaa
                                                                       180
ggctttggta aaaaaaggtt caggcattcc tagccgantg tgacacagtg gagcanaaca
                                                                       240
tctgcangag actgancggc tgca
                                                                       264
      <210> 73
      <211> 442
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(442)
      <223> n = A, T, C or G
```

```
<400> 73
ggcgaatccg gcgggtatca gagccatcag aaccgccacc atgacggtgg gcaaqaqcaq
                                                                        60
caagatgctg cagcatattg attacaggat gaggtgcatc ctgcaggacg gccggatctt
                                                                       120
cattggcacc ttcaaggctt ttgacaagca catgaatttg atcctctgtg actgtgatga
                                                                       180
gttcagaaag atcaagccaa agaacttcaa acaagcagaa agggaagaga agcgagtcct
                                                                       240
cggtctggng ctgctgccaa gggagaatct ggtctcaatg acngtagaag gaccttcttc
                                                                       300
caaagatact ggnattgctc gagttccact tgctggaact tcccggggcc caaggatcqc
                                                                       360
aaggettetg geaaaagaaa teeanaettn ggeegggaee aeetaaneea atteacaeae
                                                                       420
tggcggccgt actagtggat cc
                                                                       442
      <210> 74
      <211> 337
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(337)
      \langle 223 \rangle n = A,T,C or G
      <400> 74
ggtagcagcg tctccagagc ctgatctggg gtcccagata cccaggcagc agcagccctg
                                                                        60
gaggtaaagg gcaagctccc caatgtgagg ggagacccca ttcctggtca gccaggcttt
                                                                       120
cagaggagat agcaggtcga gggagccaac gaagaagag ctgccancag gggaaggact
                                                                       180
gtcccgccaa ggacagaact gattcagggg ggtcaatgct cctctagaga agagccacac
                                                                       240
agaactgggg ggtccaggaa ccatgaanct tggctgtggt ctaaggagcc aggaatctgg
                                                                       300
acagtgttct gggtcatacc aggattctgg aattgta
                                                                       337
      <210> 75
      <211> 588
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(588)
      <223> n = A, T, C or G
     . <400> 75
catgatgagt totgagctac ggaggaacco toatttooto aaaagtaatt tatttttaca
                                                                        60
gcttctggtt tcacatgaaa ttgtttgcgc tactgagact gttactacaa actttttaag
                                                                       120
acatgaaaag gcgtaatgaa aaccatcccg tccccattcc tcctctctc tgagggactg
                                                                       180
gagggaagcc gtgcttctga ggaacaactc taattagtac acttgtgttt gtagatttac
                                                                       240
actitigatit atgitattaac atggcgtgtt tattititgta tittitctctg gitigggagta
                                                                       300
tgatatgaag gatcaagatc ctcaactcac acatgtagac aaacattagc tctttactct
                                                                       360
ttctcaaccc cttttatgat tttaataatt ctcacttaac taattttgta agcctgagat
                                                                       420
caataagaaa tgttcaggag agangaaaga aaaaaaatat atgttcccca tttatattta
                                                                       480
gagagagacc cttantcttg cctgcaaaaa gtccaccttt catagtagta ngggccacat
                                                                       540
attacattca gttgctatag gncagcactg aactgcatta cctgggca
                                                                       588
      <210> 76
      <211> 196
      <212> DNA
```

<213> Homo sapien

```
<400> 76
geggtateae ageetggeee ceatgtaeta teggggggee eaggetgeea tegtggteta
                                                                        60
tgacatcacc aacacagata catttgcacg ggccaagaac tgggtqaaqq aqctacagaq
                                                                       120
gcaggccagc cccaacatcg tcattgcact cgcgggtaac aaggcagacc tggacctgcc
                                                                       180
cgggcggccg ctcgaa
                                                                       196
      <210> 77
      <211> 458
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (458)
      <223> n = A,T,C or G.
      <400> 77
agtagagatg gggtttcact gtgttaacca ggatggtctt gatctcctgg cctcgtgatc
                                                                        60
tgcccgcctc ggcctcccaa agtgttggga ttacaggcgt gaaccaccgc acccggccag
                                                                       120
aaatgttagt ttttccctat tctctccct ttttcctatt atatacttgg tcaaccagac
                                                                       180
agccatccta ccccanaatg gtaatgcctc ttcattcctc atatgagga ataaaagaga
                                                                       240
aaaaagcttt tggaaaacat ccacttatct aatcatccca aatatgtaat caaaagtata
                                                                       300
caactcatgt gaagaataca ctggtaaaat gttantatag gccaaggtat cttgaattcc
                                                                       360
tatatagaaa gctggtaaat gcccttttgg ctggaaccgc catcttccnn taattcnccc
                                                                       420
aaaatgacca aacacaaagg gnaagangan aagccccc
                                                                       458
      <210> 78
      <211> 464
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(464)
      \langle 223 \rangle n = A,T,C or G
      <400> 78
tccgcaaatt tcctgccggc aaggtcccag catttgaggg tgatgatgga ttctgtgtgt
                                                                        60
ttgagagcaa cgccattgcc tactatgtga gcaatgagga gctgcgggga agtactccag
                                                                       120
aggcagcagc ccaggtggtg cagtgggtga gctttgctga ttccgatata gtgcccccag
                                                                       180
ccagtacctg ggtgttcccc accttgggca tcatgcacca caacaaacag gccactgaga
                                                                       240
atgcaaagga ggaagtgagg cgaattctgg ggctgctgga tgcttacttg aagacgagga
                                                                       300
cttttctggt gggcgaacga gtgacattgg ctgacatcac agttgtctgc accctgttgt
                                                                       360
ggctctataa gcaggntcta gaaccttctt ttcgcangac cttcggccgg accacgctta
                                                                       420
acccaaattc cacacattg enggeegtac taanggaatc ccac
                                                                       464
      <210> 79
      <211> 380
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(380)
      <223> n = A,T,C or G
```

```
<400> 79
ctgtatgacc agtttttcca tctccttcac ttctaccttg atcagctcga agtccagttc
                                                                        60
agtgtaagaa atggtateet tetecatgat gteaattegg acagttaggt ttaacagttt
                                                                       120
cttttcatac acactaatta attggacata ttccctcact ttanaaagtt ctttctcaaa
                                                                       180
                                                                       240
cttctganaa aagaacatga actgtgaatt ccaagcgttc ccactctgtc cacgggaaaa
ggtggtgtct ggcagggaaa cagaacactg gcaggtccac ggtcatccac ggagccggtg
                                                                       300
aaattgggaa aacaactggg acacagaacc teegetgeet aagetgeggn tgggagettg
                                                                       360
                                                                       380
gaacccgacc tggaactgga
      <210> 80
      <211> 360
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(360)
      \langle 223 \rangle n = A,T,C or G
      <400> 80
tcgagcggcc gcccgggcag gtcctcagag agctgtttgt tncgcttctt caaaaactcc
                                                                        60
                                                                        120
tattctccac ttctqctaaa ggactggatg acatcaattg tgatagcaat atttgtgggt
                                                                        180
gttctgtcan ncancatcgc actcctgaac aaagtagatg ttggattgga tcagtctctt
tccacccaga tgactcctan atggtggatn atttcaaatc catcantcag tacctgcatg
                                                                        240
                                                                        300
cgnggtccgc ctgtgtnctt tgtcctgcag gangggcnct actacacttc ttccnagggg
canaacatgg tgtgcngcgg ccatgggctg gcaacantga ttcnctgctg cacccanatn
                                                                        360
      <210> 81
      <211> 440
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (440)
      <223> n = A,T,C or G
      <400> 81
acgtggtccg gcgagtctga cctgcagata tgaactcctt gggaaaccta cattctgcct
                                                                         60
                                                                        120
cagacatact gggggcaaat ggctttaaaa gtctggctca gggagccaag attacagaaa
nccgttgagt cnccatacat ggacactgac aaaggaactg aagatatcca aacaagccct
                                                                        180
cctggtcccg ngcctgcata aagatcggga ncggaacggt accngacgtc tgtggtcagg
                                                                        240
                                                                        300
qqttqtqqaa aattqqaaaa aaccagtcct gcccacattg acagggaagc ctcaacggaa
attgaacaga tngtcttatc accagtctcc cctcctggat cntgtctcgg ctcnggggan
                                                                        360
tcagtgatca gtcctttcag gtggaagaag caaagaagat caacaanaag cngatcctct
                                                                        420
                                                                        440
cacctgntac cagcatatgg
       <210> 82
       <211> 264
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
```

```
<222> (1)...(264)
      <223> n = A,T,C or G
      <400> 82
agcqtqqtcq cqqccqanqt cctqacattc ctqccttctt atattaatta tacnaataaa
                                                                       60
acaaaatagt gttgaagtgt tggagcggcg aaaatttttg gggggtggta tggacagaga
                                                                      120
atgggcgatn ttctcanggc tgcttcaagt gggattgggg cngcgtggga tcatncagtg
                                                                      180
gganagattn cnctgaccgg antctnttgg tanggatnat cttgtgggga tgtgcaagag
                                                                      240
ncattcgtct cctgaatgan tggt
                                                                      264
      <210> 83
      <211> 410
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(410)
      <223> n = A, T, C or G
      <400> 83
anogtggtog oggocgangt coacagttgt gggagagcca gccattgtgg gggcagctco
                                                                       60
acaggtaaqa ctcgtqtcct qaqcaqcqca catcatccaq qacaatqqqt cctqaqccct
                                                                      120
gaccaaaccg ggcatttcct ggggctgaca tggcccagcc acagcccant tgcctgcaga
                                                                      180
cgaaattggc atcattggtg tcccagtant catcacacac ggtgccccag gaacctccgg
                                                                      240
tatangaact ccacteggee tenanacetg tegeeteeat teencageet cagggggeaa
                                                                      300
actgggattc agatectict gtgggtacag gtggtgatat cetgacagge caactitetg
                                                                      360
gcctgagtgt tgactgangc tgggcagacc tgcccgggcg gccgctcgaa
                                                                      410
      <210> 84
      <211> 320
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(320)
      <223> n = A,T,C or G
      <400> 84
tegaacggcc gecegggcag gtetgeecca ggtgtateca tttgeegeeg atetetatea
                                                                       60
naaggagetg getaccetge nnegacgaan teetgaanat aateteacce neecagatet
                                                                      120
ctctgtcgca atggagatgt cgtcatcggt ggncctgatc acagggcatt ggactcagag
                                                                      180
anangthanc acagtgtnga agcgattgan nnagttcagt tgctggtctt acccgatntt
                                                                      240
ggaaggaagg aaaacgtgtt angacgtatc tcgatgnant tgaccaaanc tgaangctnc
                                                                      300
agggggcatc gcaaaganan
                                                                      320
      <210> 85
      <211> 218
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(218)
```

```
<223> n = A,T,C or G
      <400> 85
togagoggco geoogggcag gtotgctgco ogtgctggtg coattgccco atgtgaagto
                                                                        60
actgtgccag cccagaacac tggtctcggg cccgagaaga ctcctttctc caqqctntan
                                                                       120
gtatcaccac taaaatctcc aggggcacca tnganatcct gggtgtccgc aatgttqcca
                                                                       180
atgtctgtcc gcnnattggc tacccaactg ttgcatca
                                                                       218
      <210> 86
      <211> 283
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(283)
     <223> n = A, T, C or G
     <400> 86
togacttott gtgaaggttt tgganaaata tgtatcagtt cgttttattt gggtattcaa
                                                                        60
taatateett ggtgataatg etgaeteeat ggettetgae eecaaaaatt gaeeetgetg
                                                                       120
ccactggttg tagccctgag attgattttt gtagccacga ttgtttcctc gtcctctgaa
                                                                       180
gtnetggttg tantteecte tgtngggeat teceetetgt tgtantteec tetgtttgan
                                                                       240
taactaccac ggccaggaaa aacaggggca cgaaggtatg gat
                                                                       283
      <210> 87
      <211> 179
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(179)
      <223> n = A,T,C or G
      <400> 87
agcgtggtcc cggccgatgt ctttctgtgt aagtgcataa cactccacat acttgacatc
                                                                        60
cttcangtca cgggccagct nttcagcant ctctggagtg ataggctact gtntgttctn
                                                                       120
ggcaagtgtc tcaanaatac aggggtcntc tctgagatga ntttcagtcc cgaaccctc
                                                                       179
      <210> 88
      <211> 512
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (512)
      \langle 223 \rangle n = A,T,C or G
      <400> 88
tcgagcggcc gcccgggcag gtcctancan agaatcacca aatttatgga qagttaacaq
                                                                        60
gggtttaaca ggaangaagt gcctttagta agttctcaag ccagangctg gaggcagcag
                                                                       120
ctaaatcaga ggacaggatc ctcagtgaaa gtgagccatt cggggtggca tgtcactcca
                                                                       180
ggaataagca caacttanaa acaaatgatt tcgtangata gcacagtgac attggtgcac
                                                                       240
```

```
ttgtgaacct gaggccactg tgtcaaactg tgcactggtt gtgaataggg aganccaaaa
                                                                        300
attatgtcct actgggtaat gagctttcaa tgggctcgat cctctcacnc tgaaagctct
                                                                        360
gtagagcagc tcagaaccac aaccactccc aacattgacc cttctggggg tactgtctgt
                                                                        420
ggcacccaca ggaaggaget ggagatecee attaggaetg tecacccaca ettgaageea
                                                                        480
caaaactgca cctcggccgc qaccaccqct ta
                                                                        512
      <210> 89
      <211> 358
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(358)
      \langle 223 \rangle n = A,T,C or G
      <400> 89
tegageggge egecegggea ggtetgeeag tececatece agacattett tgcatetaag
                                                                         60
etgangtetg aactgagtgg ggtgggetgg tgtttccatc ctcacaactc caqtqagccg
                                                                        120
ggtgtggccg tggcctgcgt ctctctggcg gttagtgatg ttggcatcat ccaccttttt
                                                                        180
caaaacaaaa gcactggact gaagaanaat cccnccctgt ntccacccag tccatggttt
                                                                        240
ttaataaaag ggttatnnaa gttgancaag ncatcaccac acacaancct aagaacnttt
                                                                        300
ttcatcnntc cccaaaacaa accencacce tgggaactee gggegegaac caegeeta
                                                                        358
      <210> 90
      <211> 250
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(250)
      <223> n = A, T, C or G
      <400> 90
cgagcggccg cccgggcagg tctggatggg gagacggact ggaactgcgg cttcccgtgg
                                                                         60
cctgcacgca caaggctccc cacggccgcc gaccttcttc agattcgatc gtatgtgtac
                                                                        120
gcacnaagag ccaaatattg acattcacaa cttcgtggga atnttacccc anaagactgc
                                                                        180
gaccccccga tcaggcgana gcctgagcat agaagaacac cgctgtgggc ttggcactgt
                                                                        240
gggncccatc
                                                                        250
      <210> 91
      <211> 133
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (133)
      \langle 223 \rangle n = A,T,C or G
      <400> 91
tcgagcggcc gnccgggcag gtcccgggtg gttgtttgcc gaaatgggca agttcntnaa
                                                                         60
ncctgggaag gtggtgcntg tnctggctgg acgctactcc ggacgcnaag ctgtcntcgt
                                                                        120
gangancatt gat
                                                                        133
```

```
<210> 92
      <211> 232
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(232)
      <223> n = A,T,C or G
      <400> 92
agcgtggtcg cggccgangt ctgtcacttt gcgggggtag cggtcaattc caqccaccaq
                                                                        60
agcatggctg taggggcgat ctgaggtgcc atcatcaatg ttcttcacga tgacaagctt
                                                                       120
tgcgtccgga gtagcgtcca gccaggacaa gcaccacctt cccacgtntt cangaactng
                                                                       180
cccatttegg cataaceace egggacetge eegggeggne getegaaaag ee
                                                                       232
      <210> 93
      <211> 480
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(480)
      <223> n = A,T,C \text{ or } G
      <400> 93
agcgtgggtc gcggccgang tctgtangct caccggccag agaagaccac tgtgagcatt
                                                                        60
ttgccgtata tcctgccctg ccatttgttc actttttaaa ctaaaatagg aacatccgac
                                                                       120
acacaccgtt tgcatcgtct tctcccttga tattttaagc attttcccat gtcgtgagtt
                                                                       180
tctcagaaac atgttttaa caattgtact atttagtcat ngtccattta ctataattta
                                                                       240
totgaccatt tocotactgt taaaatactt aagacggttt ctgatttttc cactatttaa
                                                                       300
ataatgctgt gatgaatatc tttaaaatct tctgatttct tactttttc ccccttagat
                                                                       360
gcctggaagt ggtattttga ggtgaaagag tttgttcatt ttgaanatat ttctgtctct
                                                                       420
ctctcgacct gatgtgtana cgctcacttc cagttagcag aaccacctta gtttgtgtct
                                                                       480
      <210> 94
      <211> 472
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(472)
      <223> n = A, T, C or G
      <400> 94
tcgagcggnc gcccgggcag ggtctgatgt cantcacaac ttgaagggat gccaatgatg
                                                                       60
taccaatcon atgtgaaatc totoctotta totoctatgo tgganaaggg attacaaagt
                                                                       120
tatgtggcng ataannaatt ccatgcacct ctantcatcg atgagaatgg agttcatgan
                                                                       180
ctggtgaacn atggtatctg aacccgatac cangttttgt ttgccacgat angantagct
                                                                      240
tttatttttg atagaccaac tgtgaaccta ccacacgtct tggacnactg anntctaact
                                                                      300
atconcaggg tittattitg citgitgaac tottnoagot nitgoaaact toccaagato
                                                                      360
canatgactg antitcagat agcattitta tgattcccan ctcattgaag gtcttatnta
                                                                       420
```

```
tntcnttttt tccaagccaa ggagaccatt ggacctcggc cgcgaccacc tn
                                                                        472
      <210> 95
      <211> 309
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(309)
      <223> n = A,T,C or G
      <400> 95
tcgagcggcc gcccgggcag agtgtcgagc cagcgtcgcc gcgatggtgt tgttggagag
                                                                        60
cgagcagttc ctgacggaac tgaccagact tttccanaag tgccggacgt cgggcancgt
                                                                       120
ctatatcacc ttgaagaant atgacggtcg aaccaaaccc attccaaaga aangtactgt
                                                                       180
gganggettt ganceegeag acaacnagtg tetgttaaga actacegatn ggaaanaana
                                                                       240
anatcagcac tgtgggtgag ctccnaggga agttaataan tttcggatgg gcttattcna
                                                                       300
acctcctta
                                                                       309
      <210> 96
      <211> 371
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(371)
      <223> n = A, T, C or G
      <400> 96
togagoggeo geoogggeag gtocaccact cacctacted cogtotetat agatttgeet
                                                                        60
gttctgggca gttctcagca atggaatcct actgtgtatc tttttgtgac tggttcttta
                                                                       120
actcagcatc acattttcaa ggttcatcca tgctgcagcc tggctccgta ctggtgacag
                                                                       180
tacttcattt ctctcccct tttgttcaga ccaaggtctc cctctgtccc caaggctaaa
                                                                       240
gtgcagttgg tgtgatcatg gctcactgca gcctcaaact cctggactca aacagtcctc
                                                                       300
ccatctcagc ctcccaaagt gctgatntta taagttgcaa gccctgcacc cagcctgtat
                                                                       360
ctccagtttg t
                                                                       371
      <210> 97
      <211> 430
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(430)
      <223> n = A,T,C \text{ or } G
      <400> 97
tcgancggcc gcccgggcag gtttnttttn tttnttttt nnnngntagt atttaaagan
                                                                        60
atttattaaa tcatcttatc accaaaatgg aaacatnttc caactagaaa catgcnacca
                                                                       120
tcatcttccc cagtccagtc ncaangtcca atattttnct tgcctctgca gataaaaagt
                                                                       180
tennattttt atacceaete ttacteecee ceaaaatttt aattengtee tneectaaaa
                                                                       240
ttncnccggg taacaantta ccaaaatggc naaccaatta ttttaaanaa aagttgcncn
                                                                       300
```

```
ttnaaaangg aaactttntg gcaanttanc ctcttttccc ttcccacccc ccantttaag
                                                                        360
gggaaaacaa tggcactttg ctcttgcttn aacccaaaat tgtcttccaa aaactattaa
                                                                        420
aaatgttnaa
                                                                        430
      <210> 98
      <211> 307
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(307)
      <223> n = A, T, C \text{ or } G
      <400> 98
tenaacggcc geeenggenn gtetngenge acetgtgeet cancegtega tacetggteg
                                                                         60
attgggacan ggaanacaat ntggttttca gggaggccac anatttggag aaacggatga
                                                                        120
atteteettt atteegaant eageteettg gteteegtag anggtgatet tgaaattete
                                                                        180
ctgttttgaa aactttcttg aanaaacctt acctgctggt tgtatttggt ctcccactcg
                                                                        240
gacaagtact cgttatccnn ggtactctta atgtgcccac gtnaactccc cgggntggca
                                                                        300
actggaa
                                                                        307
      <210> 99
      <211> 207
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(207)
      <223> n = A, T, C or G
      <400> 99
gtccnggacc gatgttgcna aganntttct tggtccanta ggttcnaaaa aatgataanc
                                                                        60
naggintanc acgigaagai nintatanag tettaninaa aacneniaga teignatgae
                                                                        120
gataantcga anacnggggg aggggntgag gngaggtggn gtganggaag anntgttgat
                                                                        180
aaaagannna gntgataaga anngagc
                                                                        207
      <210> 100
      <211> 200
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(200)
      <223> n = A,T,C or G
      <400> 100
acntnnacta gaantaacag ncnttctang aacactacca tctgtnttca catgaaatgc
                                                                        60
cacacacata naaactccaa catcaatttc attgcacaga ctgactgtaa ttaattttgt
                                                                       120
cacaggaatc tatggactga atctaatgcn nccccaaatg ttgttngttt gcaatntcaa
                                                                       180
acatnnttat tccancagat
                                                                       200
      <210> 101
```

```
<211> 51
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(51)
      <223> n = A,T,C or G
      <400> 101
tcgagcggcc gcccgggcag gtctgaccag tgganaaatg cccagttatt g
                                                                         51
      <210> 102
      <211> 385
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(385)
      \langle 223 \rangle n = A,T,C or G
      <400> 102
aacgtggtcg cggccgaagt ccatggtgct gggattaatc cactgtgacn gtgactctga
                                                                         60
gttgagttgt ttttcaatct tctccaagcc tgtggactca tcctccacat ccttgggtag
                                                                        120
taggatgaac atgctgaaga tgctnatttt gaaaaggaac tctatgaatc ttacaattga
                                                                        180
atactgtcaa tgtttcccca tnacagaacg tggnccccca aggttccatc atctgcactg
                                                                        240
ggtttgggtg ttctgtcttg gttgactctt gaaaagggac atttctttt gttttcttga
                                                                        300
attcanggaa attttcttca tccactttgc ccacaaaagt taggcagcat ttaacccca
                                                                        360
anggattttg ggtctgggtc cttcc
                                                                        385
      <210> 103
      <211> 189
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(189)
      <223> n = A,T,C or G
      <400> 103
agcgtggtcg cggccgaagt ctgcagcctg ggactgaccg ggaagctctg attatttacc
                                                                         60
caccacaggt angitgigtt cigaatcica agitcacagg tiaaggciac agcatccica
                                                                        120
tcctccacgg ggttggantt gttgctggtg atgaanggtt tggggtggct ctgcataact
                                                                        180
gttgatctc
                                                                        189
      <210> 104
      <211> 181
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (181)
      \langle 223 \rangle n = A,T,C or G
```

```
<400> 104
tcgagcggcc gcccgggcag gtccaggtct ccaccaangc accaccgtgg gaagctggta
                                                                        60
attgatgccc accttgaagc cnntggggca ccatccncca actggatgct gcgcttggtt
                                                                       120
ttgatggtgg caatggcaca ttgactcttt tgggaaccac ttcaccacgg tacaacaggc
                                                                       180
                                                                       181
      <210> 105
      <211> 327
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(327)
      <223> n = A,T,C or G
      <400> 105
tcgagcggcc gcccgggcag gtcttctgtg gagtctgcgt gggcatcgtg ggcagtgggg
                                                                       60
ctgccctggc cgatgctcan aaccccagcc tctttgtaaa gattctcatc gtgganatct
                                                                       120
ttggcagcgc cattggcctc tttggggtca tcgtcgcaat tcttcanacc tccanaatga
                                                                       180
anatgggtga ctanataata tgtgtgggtn gggccgtgcc tcacttttat ttattgctgg
                                                                       240
ttttcctggg acagaactcg ggcgcgaaca cgcttanccg aattccaaca cactggcggg
                                                                       300
cgttactagt ggatccgagc tcggtac
                                                                       327
      <210> 106
      <211> 268
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(268)
      <223> n = A, T, C \text{ or } G
      <400> 106
agegtggteg eggeegangt etggegtgtg ceacateggt eccacetege titacaaaac
                                                                       60
agteetgaae tinatetaat aaaattattg tacaenacat ttacattaga aaaaganage
                                                                       120
tgggtgtang aaaccgggcc tggtgttccc tttaagcgaa ngtggctcca cagttggggc
                                                                      180
atcgtcgctt cctcnaagca aaaacgccaa tgaaccccna agggggaaaa aggaatgaag
                                                                      240
gaactgnccn gggangnccg ctccqaaa
                                                                      268
      <210> 107
      <211> 353
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(353)
      <223> n = A, T, C or G
      <400> 107
tcgagcggcc gcccgggcag gtggccaggc catgttatgg gatctcaacg aaggcaaaca
                                                                       60
cctttacacn ctagatggtg gggacatcat caacgccctg tgcttcagcc ctaaccgcta
                                                                      120
```

```
ctggctgtgt gctgccgcag gccccagcat caagatctgg gatttanagg gaaagatcnt
                                                                       180
tgtnnatgaa ctgaancnta aattatcagt tccannacca ngcaaaaacc accongtgca
                                                                       240
ctccctggcc tggtctgctg atgggacctc gggcgcgaac acgctnancc caattccanc
                                                                       300
acactgggcg gncgttacta ntggatccga actcnggtac caancttggc gtt
                                                                       353
      <210> 108
      <211> 360
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(360)
      <223> n = A,T,C or G
      <400> 108
agcgtggtcg cggccgaagt cctggcctca catgaccctg ctccagcaac ttgaacagga
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naagcagcag ctacatcctt aaggtccgga aagttagatg aagatttgga tcctgcattg
                                                                        120
nectgeetee cacetatete tecenaatta taaacageet eettgggaag cageagaatt
                                                                       180
taaaaactct cccnctgccc tnttgaacta cacaccnacc gggaaaacct ttttcanaat
                                                                       240
ggcacaaaaa tncnagggaa tgcatttcca tgaangaana aactgggtta cccaaaatta
                                                                        300
ttgggttggg gaaatccngg gggggttttn aaaaaagggc aanccnccaa anaaaaaaac
                                                                       360
      <210> 109
      <211> 101
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(101)
      \langle 223 \rangle n = A,T,C or G
      <400> 109
atcgtggtcn cggccgaagt cctgtgtcct ggatgggccg tgtgcancga atccgttggc
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gactcctaac taccaanaaa angactctcg gaagaaattt c
                                                                        101
      <210> 110
      <211> 300
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(300)
      <223> n = A, T, C or G
      <400> 110
ccanggaaac ccagagtcac atgagatagg gtggctttcg ggacaggggg tcagangaat
                                                                        60
ggtacatgga tctcagcccc tgatggacac ggaacaggtg tggtcagaac tcccangatt
                                                                       120
ctgcatccan gatccagtct ctatagaagt tatggatcat tccttcattt cattccccc
                                                                       180
ttcatgaaaa aacttctgaa caagcctttt ttctcacttt ggggccctgt ttggcncaag
                                                                       240
gtnttnantt ggggaaaaaa aaacaaatcc nttccnttan ccctccgtgg ggaatgacct
                                                                       300
```

<213> Homo sapien

```
<211> 366
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(366)
     <223> n = A, T, C \text{ or } G
     <400> 111
cgagcggccg cccgggcagg tccttgtgtt gccatctgtt ancattgatt tctggaatgg
                                                                     60
aacanctttc tcaaagtttg gtcttgctan tcatgaagtc atgtcagtgt cttaagtcac
                                                                    120
tgctgctcac ttccttaccc agggaatata ctgcataagt ttctgaacac ctgttttcan
                                                                    180
tattcactgt tectetectg eccaaaattg gaagggacet cattraaaaa teaaatttga
                                                                    240
atcctgaaan aaaaacngga aatntttctc ttggaatttg gaatagaatt attcanttga
                                                                    300
ataacatgtt ttttcccctt gccttgctct tcncaanaac atctggacct cggccgcgac
                                                                    360
acctta
                                                                    366
     <210> 112
     <211> 405
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(405)
     <223> n = A,T,C or G
     <400> 112
ctgactncta aacttctaat tcnatcaana taactactct ccttccgtct tncagagtgt
                                                                     60
tcacaataaa tctgtgaatc tggcatacac agttgctgga aaattgttct tcctccacna
                                                                    120
aaaggtcaat tgttcnccnc atgaaanaag ataaattgtt catccatcac tnctgaacca
                                                                    180
tccaaaacgc cggcggaatt attnccccgt tattatgggg aacggaattt tnaataaatt
                                                                    240
tgggaangaa tggggctttt attgttttgt tttccccctt tcttggcatt gattgggccq
                                                                    300
caatgggccc cctcgctcan aanntgcccc ggggccggcc gctccaaaac cgaaattccc
                                                                    360
anccacactt ggcgggccgt tactanttgg atccgaactc ggtta
                                                                    405
     <210> 113
     <211> 401
     <212> DNA
     <213> Homo sapien
     <400> 113
ggatagaaga gtatatgggt ttggcaccac ggggtggata ggcaaaacat ttggttgata
                                                                     60
aggcgcagat tctgaactaa cttgtaaggc ttgtctggtt ttaggacagg taaaatgggg
                                                                    120
gaatggtaag gagagtttat aggttttagg agcccatgct gtagcaggca agtgataaca
                                                                    180
ggctttaatc ctttcaaagc atgctgtggg atgagatatt ggcatttgag cggggtaagg
                                                                    240
300
tagaggtatc ttatacttgt ggggttaagg tgggggggat ataagaggga ggacgccaaa
                                                                    360
ggaggctttg gattaggaat aaggggcggc aatgagatgc a
                                                                    401
     <210> 114
     <211> 401
     <212> DNA
```

```
<220>
      <221> misc_feature
      <222> (1)...(401)
      <223> n = A, T, C or G
      <400> 114
angtecacag gangeangag gecaggetee gteceancea gtecatgatg ttgaagagga
                                                                        60
ggaagcagca catggggttg aagaactgac tecaetteec aggactggtg gagetggtea
                                                                       120
ccatggctgt ggtggcgggg aagacggaca gggtgacttc tggaagacag tgaagactga
                                                                       180
aggttttcct ggcttctggg gctcatctgg ctctgattcc ggctccttct ccaggtcaag
                                                                       240
atccagggtt cagagctact ttcttggggg actactnggg aatcccgttc tcatctgggg
                                                                       300
gtngaggggg gacggggnaa gggncatgct tgtgacccag gtttcccacc tcggcccgcg
                                                                       360
accacgctaa ggcccgaatt ncagcacact tggcggcccg t
                                                                       401
      <210> 115
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 115
atccctgtaa gtctattaaa tgtaaataat acatacttta caacttctct tagtcggccc
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ttggcagatt aaatctttgc aaaattccat atgtgctatt gaaaaatgaa ataaaacctc
                                                                       120
agatgtctga attcttattt caaatacagt tatataatta ttttaaatta caatatacaa
                                                                       180
tttctgttaa atacaactgt taagggattc tgagaacaat tataagatta taataatata
                                                                       240
tacaaactaa cttctgaaat gacatgggtt gtttccttcc caccctccta ccctctcaaa
                                                                       300
gagtttttgc atttgctgtt cctggttgca aaaggcaaaa gaaaatctaa aaatagtctg
                                                                       360
tgtgtgtcca cgacatgctc gctcctttga gaatctcaaa c
                                                                       401
      <210> 116
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A,T,C or G
      <400> 116
ngatttaatt gnnagcttct ttttaatgga atnnttggct aaaatgaatt gatgattatg
                                                                       60
aatatcccta ggaggagtta gcatggannn tgatcatttt cttngnactc ctttangaca
                                                                      120
nggaaacagg natcagcatg anggtancan aaaccttatn accnangege acganetgae
                                                                      180
ttcttccaaa gagttgnggt tccgggcagc ggtcattgcc gtgcccattg ctggagggct
                                                                      240
gattctagtg ntgcttatta tgctggccct gaggatgctt ccaanatgaa aataagangc
                                                                      300
                                                                      301
      <210> 117
      <211> 383
      <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
      <222> (1)...(383)
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<223> n = A,T,C or G <400> 117 aattgcaact ggacttttat tgggcagtta cnacaacnaa tgttttcana aaaatatttg 60 gaaaaaatat accacttcat agctaagtct tacagaqaan aggatttgct aataaaactt 120 aagttttgaa aattaagatg cnggtanagc ttctgaacta atgcccacag ctccaaqqaa 180 nacatgteet atttagttat teaaatacea gttgagggea ttgtgattaa geaaacaata 240 tatttgttan aactttgntt ttaaattact gntncttgac attacttata aaggagnctc 300 taactttcga tttctaaaac tatgtaatac aaaagtatan ntttccccat tttgataaaa 360 gggccnanga tactgantag gaa 383 <210> 118 <211> 301 <212> DNA <213> Homo sapien <400> 118 ctgctagaat cactgccgct gtgctttcgt ggaaatqaca qttccttqtt ttttttqttt 60 ctgtttttgt tttacattag tcattggacc acagccattc aggaactacc ccctqcccca 120 caaagaaatg aacagttgta gggagaccca gcagcacctt tcctccacac accttcattt 180 tgaagttcgg gtttttgtgt taagttaatc tgtacattct gtttgccatt gttacttqta 240 ctatacatct gtatatagtg tacggcaaaa gagtattaat ccactatctc tagtgcttga 300 С 301 <210> 119 <211> 401 <212> DNA <213> Homo sapien <400> 119 taaggacatg gacccccggc tgattgcatg gaaaggaggg gcagtgttgg cttgtttgga 60 tacaacacag gaactgtgga tttatcagcg agagtggcag cgctttggtg tccgcatgtt 120 acgagagegg gctgcgtttg tgtggtgaat ggggaggaaa tgtcactgcc gaagaccaaa 180 aacaagcttc ttggtataaa agactcttac agaatatgtg tattgtaatt tattgatctg 240 gatgcttaag tgtcatggac agtaaatgaa tttgaacttt atgtttgagg acatgacatt 300 gggtttgaaa atataaactg cttttgagca gtttaagtca gggcatttga gaataaaata 360 ggaactttct cttcagtttg taaaactctc ttgccctctc t 401 <210> 120 <211> 301 <212> DNA <213> Homo sapien <400> 120 tccagagata ccacagtcaa acctggagcc aaaaaggaca caaaggactc tcgacccaaa 60 ctgccccaga ccctctccag aggttggggt gaccaactca tctggactca gacatatgaa 120 gaagctctat ataaatccaa gacaagcaac aaacccttga tgattattca tcacttgggt 180 gagtgcccac acagtcaagc tttaaagaaa gtgtttgctg aaaataaaga aatccagaaa 240 ttggcagagc agtttgtcct cctcaatctg gtttatgaaa caactgacaa acacctttct 300 C 301

<210> 121 <211> 2691 <212> DNA

<213> Homo sapien

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ccgccaagtc gccctaccag ctggtgctgc agcacagcag gctccggggc cgccagcacg
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gccccaacgt gtgtgctgtg cagaaggtta ttggcactaa taggaagtac ttcaccaact
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gtcctggata tgaaaaggtc cctggggaga agggctgtcc agcagcccta ccactctcaa
                                                                       360
acctttacga gaccctggga gtcgttggat ccaccaccac tcagctgtac acggaccgca
                                                                       420
cggagaaget gaggeetgag atggaggge eeggeagett caccatette geeetagea
                                                                       480
acgaggeetg ggeeteettg ceagetgaag tgetggaete eetggteage aatgteaaca
                                                                       540
ttgagetget caatgeeete egetaecata tggtgggeag gegagteetg actgatgage
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tgaaacacgg catgaccete acctetatgt accagaatte caacatecag atceaccact
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ccaacggggt ggtgcacctc atcgataagg tcatctccac catcaccaac aacatccagc
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ctccaattga tgcccataca aggaatttgc ttcggaacca cataattaaa gaccagctgg
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cctctaagta tctgtaccat ggacagaccc tggaaactct gggcggcaaa aaactgagag
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gggggaggta cgggaccetg ttcacgatgg accgggtget gacceccca atggggactg
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tcatggatgt cctgaaggga gacaatcgct ttagcatgct ggtagctgcc atccagtctg
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                                                                     1860
tggtgagtgt caacaaggag cetgttgeeg ageetgacat catggeeaca aatggegtgg
                                                                     1920
tecatgical caccaatgit eigeageete cagecaacag aceteaggaa agagggatg
                                                                     1980
aacttgcaga ctctgcgctt gagatcttca aacaagcatc agcgttttcc agggcttccc
                                                                     2040
agaggtetgt gegaetagee eetgtetate aaaagttatt agagaggatg aageattage
                                                                     2100
ttgaagcact acaggaggaa tgcaccacgg cagctctccg ccaatttctc tcagatttcc
                                                                     2160
acagagactg tttgaatgtt ttcaaaacca agtatcacac tttaatgtac atgggccgca
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ccataatgag atgtgagcct tgtgcatgtg ggggaggagg gagagagatg tacttttaa
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atcatgttcc ccctaaacat ggctgttaac ccactgcatg cagaaacttg gatgtcactg
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cctgacattc acttccagag aggacctatc ccaaatgtgg aattgactgc ctatgccaag
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attataagct atgagttgaa atgttctgtc aaatgtgtct cacatctaca cgtggcttgg
                                                                     2580
aggettttat ggggeeetgt eeaggtagaa aagaaatggt atgtagaget tagattteee
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```

<210> 122

<211> 683

<212> PRT

<213> Homo sapien

<400> 122

Met Ala Leu Phe Val Arg Leu Leu Ala Leu Ala Leu Ala Leu

1				5					10					1 5	
_	Pro	Ala	Ala	_	Leu	Ala	Glv	Pro		Lvs	Ser	Pro	Tvr	15 Gln	Leu
•			20				1	25		-3-			30	0	Deu
Val	Leu	Gln 35	His	Ser	Arg	Leu	Arg 40	Gly	Arg	Gln	His	Gly 45	Pro	Asn	Val
Cys	Ala 50	Val	Gln	Lys	Val	Ile 55	Gly	Thr	Asn	Arg	Lys 60	Tyr	Phe	Thr	Asn
Cys 65	Lys	Gln	Trp	Tyr	Gln 70	Arg	Lys	Ile	Cys	Gly 75	Lys	Ser	Thr	Val	Ile 80
Ser	Tyr	Glu	Cys	Cys 85	Pro	Gly	Tyr	Glu	Lys 90	Val	Pro	Gly	Glu	Lys 95	Gly
Схв	Pro	Ala	Ala 100	Leu	Pro	Leu	Ser	Asn 105	Leu	Tyr	Glu	Thr	Leu 110	Gly	Val
Val	Gly	Ser 115	Thr	Thr	Thr	Gln	Leu 120		Thr	Asp	Arg	Thr 125	Glu	Lys	Leu
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44

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tcaggtcagg tagagtcaaa atcaggcacc ccgactcaca gactgcttca cattgccatc	120
agagattgtc ctgcaacaat attatgttta gttctactgc agaatgataa ctggatctta	180
ccccctttgc ctgatctggc cacaaacttg tttttcaggt ctttccatta ggctctcttc	240
agctaatt	248
222	
-210 142	

<210> 142

<211> 173

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<212> DNA
     <213> Homo sapien
     <400> 142
tactaagatt gtccaagcct ccctcttaaa actttctttc cctttagagg aatcattact
                                                                        60
togtattaaa agtttotact toottgtaga atatotacat ccaatgggco atggcacaaa
                                                                       120
                                                                       173
atttaagtct agaaagaatc ttaaaggctc atcttatagt aaccagaggc agg
      <210> 143
      <211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(511)
      \langle 223 \rangle n = A,T,C or G
      <400> 143
cctcgtcaga ggggtggttc ctggtnacct gtactccacg gacctcggtg aagcaaaagc
                                                                        60
ttcagggcag agggaatgag gcaacccagt ggcagccccg ctgggccccg tggctcctgc
                                                                        120
totoctattg gacgtagagg caggggagag acttototat acaaatatto toatoacaga
                                                                        180
agggatgate ettgetgete tgeegtaggg tttttgatge tgagetatge tgeacatgae
                                                                       240
gttaacctaa agaacttgga ctgagctttt aaaaaaggac agcaaacaat tttataatcc
                                                                       300
ttaaagtgta atagacggtt acactagtgc agggtattgg ggaggctctt tgggtgtgga
                                                                       360
ggctgtcact tgtatttatt gtgactctaa atctttgata gtaaaacaaa tgtaaaaaga
                                                                       420
aatgtttgcc accagatggg aatagaagtt ccaataagca ggctggaatg ggtggctata
                                                                       480
cgttgtatca cgaggaagtt ttagactctg a
                                                                        511
      <210> 144
      <211> 190
      <212> DNA
      <213> Homo sapien
      <400> 144
cattettetg teacatgeea atteagttgt caateceatt gtetatgett aceggaaceg
                                                                        60
agacttccgc tacacttttc acaaaattat ctccaggtat cttctctgcc aagcagatgt
                                                                        120
caagagtggg aatggtcagg ctggggtaca gcctgctctc ggtgtgggcc tatgatctag
                                                                        180
gctctcgcct
                                                                        190
      <210> 145
      <211> 169
      <212> DNA
      <213> Homo sapien
      <400> 145
gatgtggtta tctcctcaga tggccagttt gccctctcag gctcctggga tggaaccctg
                                                                         60
cgcctctggg atctcacaac gggcaccacc acgaggcgat ttgtgggcca taccaaggat
                                                                        120
gtgctgagtg tggccttctc ctctgacaac cggcagattg tctctggat
                                                                        169
      <210> 146
      <211> 511
      <212> DNA
      <213> Homo sapien
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<212> DNA

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<400> 146
atctagagaa gatttgggaa acacatgata gctatggtta aatacttaac agggcaatca
                                                                        60
cagggaagat gactagattt cctaacatcc atgagtgaaa tttatagaag tatactctct
                                                                       120
gacttgatat aaaggaagat tttaaaaaaac atgactgttc aggagtgttc aagtagggtc
                                                                       180
agatgaccag tgattgggaa tacttcgtaa gcaggagcaa gtaagatctg agccactgtt
                                                                       240
ctatcggtag ggtgtctgtg gtattccttg gtcaaagaag tactctaagc aacttcaqtc
                                                                       300
tcacgaatta ctatcaccct cgtgggcata catgatggtt accctaaaga ggaaqtttca
                                                                       360
gaaggcagta atattggatc ctggaatagt cagacaggag ccttcatgca gatacccttt
                                                                       420
tcagttctcc atacacccat tcacaagtgg tcacaaaaac acccagtacc tttacttggc
                                                                       480
tttacccact taacaatatg ctcaatatga g
                                                                       511
      <210> 147
      <211> 421
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(421)
      <223> n = A, T, C or G
      <400> 147
gaccagttga gttcttcctg gctattgtat aatccacagc cacactgtga aagcaaatct
                                                                       60
ggccagttag caacacaggg agaatetgcc tgaactgacc aaaggtgtcc atacttcatg
                                                                       120
tcagtgagaa tttcacctcc atcatgttct aaagagccaa caacagattc tagggcactq
                                                                       180
caaaatgctt cagcaattaa ttgaagttct gtttgagtac attcatcatc tttgagaatg
                                                                       240
ctttctgggt cgttgtgagt cttgtgtctg atatatgcag ccaaatgagt ttcagtacag
                                                                       300
ccacctccca acaaagccca tggttccttg agtgttaact gcaggacatg cagtgccgtc
                                                                       360
tgacacgtga gcttcagctc atcccangca gtgtcatttc tgttgcagag aagccaagct
                                                                       420
                                                                      421
      <210> 148
      <211> 237
      <212> DNA
      <213> Homo sapien
      <400> 148
acacaccact gttggccttc catctgggtt aagtcaactg tgagtagaaa ccgaagataa
                                                                       60
cagttttgta ttcataatgg ccttttcata ctccaagtac ttttgagcac agagcctctt
                                                                       120
gcttctgacc tggcacttgg aacacagata tatatatctt ttgttctgtc cctgggaaac
                                                                      180
tgatatttgt gtaagacaac caccagatat tttctctaat aaaatcttct aaaatta
                                                                      237
      <210> 149
      <211> 168
      <212> DNA
      <213> Homo sapien
      <400> 149
agagaaagtt aaagtgcaat aatgtttgaa gacaataagt ggtggtgtat cttgtttcta
                                                                       60
ataagataaa cttttttgtc tttgctttat cttattaggg agttgtatgt cagtgtataa
                                                                      120
aacatactgt gtggtataac aggcttaata aattctttaa aaggagag
                                                                      168
      <210> 150
      <211> 68
```

```
<213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(68)
      <223> n = A,T,C or G
      <400> 150
ggtggggttt ggcagagatg antttaagtg ctgtggccag aagcgggggg ggggtttggt
                                                                        60
ggaaattt
                                                                        68
      <210> 151
      <211> 421
      <212> DNA
      <213> Homo sapien
      <400> 151
aggtgacacg tattcgggat gaaagtataa tagtcattcc ttcaaccctt gcatttatgg
                                                                        60
actctggaaa tcgaagatcc acagtgagta aagatgttcg tccaaagaca aaaaatagaa
                                                                       120
acageteaac aaagegagag acaaaaaaac aaaatggcac tgtggetetg cetttqaaqt
                                                                       180
ctgggctcca gcagagggct gatcttccca caggagacga gacggcctat qacactctcc
                                                                       240
agaactgttg tcagtgccga attttacttc ccttgcccat tctaaatgag caccaggaga
                                                                       300
agtgccagag gttagctcac caaaagaaac tccagtgggg ctggtgagat gqctcaqcqq
                                                                       360
gtaagagcac ccgactgctc ttccgaaggt ccggagttca aatcccagca accacatggt
                                                                       420
g
                                                                       421
      <210> 152
      <211> 507
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(507)
      \langle 223 \rangle n = A,T,C or G
      <400> 152
gaattcggca cnagctcgtg ccgccagggt nggtccnttt tttgctccgc ctcgccanga
                                                                   . 60
cttcctacag ctatcgccag tcgtcggcca cgtcntcctt cngaggcctg ggcggcggct
                                                                       120
ccgtgcgttn tgggccgggg gtcgcctttc nctcncccag cattcacggg ggctccggcg
                                                                       180
gccgcggcgt atccgtgtcc tccgcccgct ntgtgtcctc gtcctcctcn ggggcctacg
                                                                       240
gctngctgct acngcggctt cctgaccgct tccnacgggc tgctggcngg caacgagaag
                                                                       300
ctaaccatgc agaacctnaa cnaccgcctg gcctcctacc tgnacaaggt gcgcnccctg
                                                                       360
taggcggcca acggcnagct agaggtgaag atccnctact gggtaccaga agcagggcc
                                                                       420
tgggccctgc ccgactacag ccactnctnc acnaccatgc agtacctgcn ggganaagat
                                                                       480
tntngggngc caccatngag aactgca
                                                                       507
      <210> 153
      <211> 513
      <212> DNA
      <213> Homo sapien
      <400> 153
gaattcggca cgaggtggct cagatgtcca ctactgggag tatggtcgaa ttgggaattt
                                                                        60
tattgtgaaa aagcccatgg tgctgggaca tgaagcttcg ggaacagtcg aaaaagtggg
                                                                       120
```

```
atcatcggta aagcacctaa aaccaggtga tcgtgttgcc atcgagcctg gtgctccccq
                                                                       180
agaaaatgat gaattetgea agatgggeeg atacaatetg teacetteea tettettetq
                                                                       240
tgccgcgccc cccgatgacg ggaacctctg ccggttctat aagcacaatg cagccttttg
                                                                       300
ttacaagett cetgacaatg teacetttga ggaaggegee etgategage eactttetgt
                                                                       360
ggggatccat gcctgcagga gaggcggagt taccctggga cacaaggtcc ttqtqtqqq
                                                                       420
agctgggcca atcgggatgg tcactttgct cgtggccaaa gcaatgggag cagctcaagt
                                                                       480
agtggtgact gatctgtctg ctacccgatt gtc
                                                                       513
      <210> 154
      <211> 507
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (507)
      <223> n = A,T,C or G
      <400> 154
ggcacgagct cgtgccgaat tcggcncgag cagacacaat ggtaagaatg gtgcctgtcc
                                                                       60
tgctgtctct gctgctgctt ctgggtcctg ctgtccccca ggagaaccaa gatggtcgtt
                                                                       120
actototgac ctatatotac actgggctgt ccaagcatgt tgaagacgtc cccgcgtttc
                                                                      180
aggcccttgg ctcactcaat gacctccagt tctttagata caacagtaaa gacaggaaqt
                                                                      240
ctcagcccat gggactctgg agacaggtgg aaggaatgga ggattggaag caggacagcc
                                                                       300
aacttcagaa ggccagggag gacatcttta tggagaccct gaaagacatc gtggagtatt
                                                                       360
acaacgacag taacgggtct cacgtattgc agggaaggtt tggttgtgag atcgagaata
                                                                      420
acagaagcag cggagcattc tggaaatatt actatgatgg aaaggactac attgaattca
                                                                      480
acaaagaaat cccagcctgg gtcccct
                                                                      507
      <210> 155
      <211> 507
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(507)
      <223> n = A,T,C or G
      <400> 155
ggcacgagga gacctaaggg ctgagtntcg ggaacaggag aaaqctctqt tqqccctcca
                                                                       60
gcagcagtgt gctgagcagg cacaggagca tgaggtggag accagggccc tgcaggacag
                                                                      120
ctggctgcag gcccaggcag tgctcaagga acgggaccag gagctggaag ctctgcgqqc
                                                                      180
agaaagtcag tcctcccggc atcaggagga ggctgcccgg gcccgggctg aggctctgca
                                                                      240
ggaggccctt ggcaaggctc atgctgccct gcaggggaaa gagcagcatc tcctcgagca
                                                                      300
ggcagaattg agccgcagtc tggaggccag cactgcaacc ctgcaagcct ccctggatqc
                                                                      360
ctgccaggca cacagtcggc agctggagga ggctctgagg atacaaqaag gtgagatcca
                                                                      420
ggaccaggat ctccgatacc aggaggatgt gcagcagctg cagcaggcac ttgcccagag
                                                                      480
ggatgaagag ctgagacatc agcagga
                                                                      507
      <210> 156
      <211> 509
      <212> DNA
      <213> Homo sapien
```

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<220>
      <221> misc feature
      <222> (1)...(509)
      <223> n = A,T,C or G
      <400> 156
ggcacgagga cagagagaac cctgtngaaa gagcgttacc aggaggtcct ggacaaacag
                                                                        60
aggcaagtgg agaatcagct ccaagtgcaa ttaaagcagc ttcagcaaag gagagaagag
                                                                        120
gaaatgaaga atcaccagga gatattaaag gctattcagg atgtgacaat aaagcgggaa
                                                                       180
gaaacaaaga agaagataga gaaagagaag aaggagtttt tgcagaagga gcaggatctg
                                                                       240
aaagctgaaa ttgagaagct ttgtgagaag ggcagaagag aggtgtggga aatggaactg
                                                                       300
gatagactca agaatcagga tggcgaaata aataggaaca ttatggaaga gactgaacgg
                                                                       360
gcctggaagg cagagatett atcactagag agccggaaag agttactggt actgaaacta
                                                                       420
gaagaagcag aaaaagaggc agaattgcac cttacttacc tcaagtcaac tcccccaaca
                                                                       480
ctggagacag ttcgttccaa acaggagtg
                                                                       509
      <210> 157
      <211> 507
      <212> DNA
      <213> Homo sapien
      <400> 157
ggcacgaggg cagccetect accggcgcac gtggtgccgc cgctgctgcc tcccgctcgc
                                                                        60
cctgaaccca gtgcctgcag ccatggctcc cggccagctc gccttattta gtgtctctga
                                                                       120
caaaaccggc cttgtggaat ttgcaagaaa cctgaccgct cttggtttga atctggtcgc
                                                                       180
ttccggaggg actgcaaaag ctctcaggga tgctggtctg gcagtcagag atgtctctga
                                                                       240
gttgacggga tttcctgaaa tgttgggggg acgtgtgaaa actttgcatc ctgcagtcca
                                                                       300
tgctggaatc ctagctcgta atattccaga agataatgct gacatggcca gacttgattt
                                                                       360
caatcttata agagttgttg cctgcaatct ctatcccttt gtaaagacag tggcttctcc
                                                                       420
aggtgtaagt gttgaggagg ctgtggagca aattgacatt ggtggagtaa ccttactgag
                                                                       480
agctgcagcc aaaaaccacg ctcgagt
                                                                       507
      <210> 158
      <211> 507
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(507)
      <223> n = A, T, C \text{ or } G
      <400> 158
ggcacgagtc gagctgtgcc tattcgngtc aatccaagag tgagtaatgt gaagtctgtc
                                                                        60
tacaaaaccc acattgatgt cattcattat cggaaaacgg atgcaaaacg tctgcatggc
                                                                       120
cttgatgaag aagcagaaca gaaacttttt tcagagaaac gtgtggaatt gcttaaggaa
                                                                       180
ctttccagga aaccagacat ttatgagagg cttgcttcag ccttggctcc aagcatttat
                                                                       240
gaacatgaag atataaagaa gggaattttg cttcagctct ttggcgggac aaggaaggat
                                                                       300
tttagtcaca ctggaagggg caaatttcgg gctgagatca acatcttgct gtgtggcgac
                                                                       360
cctggtacca gcaagtccca gctgctgcag tacgtgtaca acctcgtccc caggggccag
                                                                       420
tacacginity ggaagggete cagigeanni ggeetnacty entacgiaat gaaagaceet
                                                                       480
gagacaaggn anctggnnct gnnacag
                                                                       507
      <210> 159
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<210> 159 <211> 508

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<212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(508)
      <223> n = A, T, C or G
      <400> 159
ggcacnanaa accaggatta tggtnnggat ccaaagattg ctaatgcaat aatgaaggca
                                                                        60
gragatyagg tagetyaagg taaattaaat gateatttte etetegtggt atggeagaet
                                                                       120
ggatcaggaa ctcagacaaa tatgaatgta aatgaagtca ttagcaatag agcaattgaa
                                                                       180
atgttaggag gtgaacttgg cagcaagata cctgtgcatc ccaacgatca tgttaataaa
                                                                       240
agccagaget caaatgatae tttteecaca geaatgeaca ttgetgetge aataqaagtt
                                                                       300
catgaagtac tgttaccagg actacagaag ttacatgatg ctcttgatgc aaaatccaaa
                                                                       360
gagtttgcac agatcatcaa gattggacgt actcatactc aggatgctgt tccacttact
                                                                       420
cttgggcagg aatttagtgg ttatgttcaa caagtaaaat atgcaatgac aagaataaaa
                                                                       480
gctgccatgc caagaatcta tgagctcg
                                                                       508
      <210> 160
      <211> 508
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(508)
      <223> n = A,T,C or G
      <400> 160
ggcacgagct tggagcaaag tcatctnaag gaattagagg acacacttca ggttaggcac
                                                                        60
atacaagagt ttgagaaggt tatgacagac cacagagttt ctttggagga attaaaaaaag
                                                                       120
gaaaaccaac aaataattaa tcaaatacaa gaatctcatg ctgaaattat ccaggaaaaa
                                                                       180
gaaaaacagt tacaggaatt aaaactcaag gtttctgatt tgtcagacac gagatgcaag
                                                                       240
ttagaggttg aacttgcgtt gaaggaagca gaaactgatg aaataaaaat tttgctggaa
                                                                       300
gaaagcagag cccagcagaa ggagaccttg aaatctcttc ttgaacaaga gacagaaaat
                                                                       360
ttgagaacag aaattagtaa actcaaccaa aagattcagg ataataatga aaattatcag
                                                                       420
gtgggcttag cagagctaag aactttaatg acaattgaaa aagatcagtg tatttccgag
                                                                       480
ttaattagta gacatgaaga agaatcta
                                                                       508
      <210> 161
      <211> 507
      <212> DNA
      <213> Homo sapien
      <400> 161
ggcacgagcg ctaccggcgc ctcctctgcg gccactgagc cggagccggc ctgagcagcg
                                                                       60
ctctcggttg cagtacccac tggaaggact taggcgctcg cgtggacacc gcaagcccct
                                                                       120
cagtageete ggeccaagag geetgettte caetegetag eeeegeggg ggteegtgte
                                                                       180
ctgtctcggt ggccggaccc gggcccgagc ccgagcagta gccggcgcca tgtcggtggt
                                                                      240
gggcatagac ctgggcttcc agagctgcta cgtcgctgtg gcccgcgccg gcggcatcga
                                                                      300
gactatcgct aatgagtata gcgaccgctg cacgccggct tgcatttctt ttggtcctaa
                                                                      360
gaatcgttca attggagcag cagctaaaag ccaggtaatt tctaatgcaa agaacacagt
                                                                      420
ccaaggattt aaaagattcc atggccgagc attctctgat ccatttgtgg aggcagaaaa
                                                                      480
atctaacctt gcatatgata ttgtgca
                                                                      507
```

<211> 462 <212> DNA

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<210> 162
      <211> 507
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(507)
      <223> n = A, T, C or G
      <400> 162
                                                                        60
ggcacgagca gctgtgcacc gacatgntct cagtgtcctg agtaagacca aagaagctgg
                                                                       120
caaqatcctc tctaataatc ccagcaaggg actggccctg ggaattgcca aagcctggga
qctctacqqc tcacccaatg ctctqqtqct actgattqct caaqaqaaqg aaaqaaacat
                                                                       180
atttqaccaq cqtqccataq aqaatqagct actggccagg aacatccatg tgatccgacg
                                                                       240
aacatttqaa qatatctctg aaaaggggtc tctggaccaa gaccgaaggc tgtttgtgga
                                                                       300
tggccaggaa attgctgtgg tttacttccg ggatggctac atgcctcgtc agtacagtct
                                                                       360
acaqaattqq qaaqcacqtc tactqctgga gaggtcacat gctgccaagt gcccagacat
                                                                       420
tgccacccag ctggctggga ctaagaaggt gcagcaggag ctaagcaggc cgggcatgct
                                                                       480
ggagatgttg ctccctggcc agcctga
                                                                       507
      <210> 163
      <211> 460
      <212> DNA
      <213> Homo sapien
      <400> 163
                                                                        60
qqcacqaqaa ataactttat ttcattgtgg gtcgcggttc ttgtttgtgg atcgctgtga
                                                                       120
tegteactig acaatgeaga tettegtgaa gaetetgaet ggtaagaeca teaccetega
ggttgagccc agtgacacca tcgagaatgt caaggcaaag atccaagata aggaaggcat
                                                                       180
ccctcctgac cagcagaggc tgatctttgc tggaaaacag ctggaagatg ggcgcaccct
                                                                       240
                                                                       300
gtctgactac aacatccaga aagagtccac cctgcacctg gtgctccgtc tcagaggtgg
gatgcaaatc ttcgtgaaga cactcactgg caagaccatc acccttgagg tggagcccag
                                                                       360
                                                                       420
tgacaccatc gagaacgtca aagcaaagat ccaggacaag gaaggcattc ctcctgacca
                                                                       460
gcagaggttg atctttgccg gaaagcagct ggaagatggg
      <210> 164
      <211> 462
      <212> DNA
      <213> Homo sapien
      <400> 164
ggcacgagec ggateteatt gccacgegec cecgacgace gecegaegtg catteecgat
                                                                        60
tccttttggt tccaagtcca atatggcaac tctaaaggat cagctgattt ataatcttct
                                                                       120
aaaggaagaa cagaccccc agaataagat tacagttgtt ggggttggtg ctgttggcat
                                                                       180
ggcctgtgcc atcagtatct taatgaagga cttggcagat gaacttgctc ttgttgatgt
                                                                       240
                                                                       300
catcgaagac aaattgaagg gagagatgat ggatctccaa catggcagcc ttttccttag
aacaccaaag attgtctctg gcaaagacta taatgtaact gcaaactcca agctggtcat
                                                                       360
tatcacggct ggggcacgtc agcaagaggg agaaagccgt cttaatttgg tccagcgtaa
                                                                       420
cgtgaacatc tttaaattca tcattcctaa tgttgtaaaa ta
                                                                       462
      <210> 165
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<213> Homo sapien

```
<400> 165
ggcacgagga agccatgagc agcaaagtct ctcgcgacac cctqtacqaq qcqqtqcqqq
                                                                        60
aagteetgea egggaaceag egcaagegee geaagtteet ggagaeggtg qaqttqeaqa
                                                                       120
tcagcttgaa gaactatgat ccccagaagg acaagcgctt ctcgggcacc gtcaggctta
                                                                       180
agtocactor regreetaag ttetetgtgt gtgtcetggg ggaccagcag caetgtgacg
                                                                       240
aggctaaggc cgtggatatc ccccacatgg acatcgaggc gctgaaaaaa ctcaacaaga
                                                                       300
ataaaaaact ggtcaagaag ctggccaaga agtatgatgc gtttttggcc tcagagtctc
                                                                       360
tgatcaagca gattccacga atcctcggcc caggtttaaa taaggcagga aagttccctt
                                                                       420
ccctgctcac acacaacgaa aacatggtgg ccaaagtgga tg
                                                                       462
      <210> 166
      <211> 459
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(459)
      \langle 223 \rangle n = A,T,C or G
      <400> 166
ggcacgagag ggacctgtnt gaatggntcc actagggttn anntgnctct tacttttaac
                                                                        60
cantnaaatn gacctgcccg tgaanangcg ggcntgacac annaanacga gaagacccta
                                                                       120
tggagcttta atttattaat gcanacagna cctaacaaac ccacangtcc taaactacca
                                                                       180
agcctgcatt aaaaatttcg gntggggcna cctcnnagca naacccaacc tccgagcaac
                                                                       240
tcatgctaag acttcaccag tcaaagctga actactatac tcaattgatc caataacttq
                                                                       300
accaacagan caagntaccc tagggataac ancacaatcc tattctagac cccttatnac
                                                                       360
caatangntt tacacctcna tngnggaacc aggacatccg atggggcagn cgttattaaa
                                                                       420
gttngttgnt aacnataaag tctacgtgat ctgagttag
                                                                       459
      <210> 167
      <211> 464
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(464)
      <223> n = A,T,C or G
      <400> 167
gaattgggac caacganaan cntgcggntc ttnttttgcn tccanngccc agctnattgc
                                                                        60
tcagacacac atggggaagg tnaaggtcgg gagtcaacng atttggtngt attgnaqcgt
                                                                       120
ttggtcacca gngctgcttt taactctggn aaagtggata ttgttgtcat naatgacccc
                                                                       180
theattgace thaactacat ggtttacatg ttecaatatg attecaceca tggcaaatte
                                                                       240
catngcaccg tnaaggctga gaacgggaag cttgtnatca atggaaatcc catcaccatc
                                                                       300
tttcangaac ganatcentn caaaaatcaa anttggggge gatgettgge enettgaagt
                                                                       360
accepticaan gegaannice ceaetitege centititie aaneeeaece caatitegen
                                                                       420
aaaaaaaaa gggnntttgg gggggggcct tttanntttt tttt
                                                                       464
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<210> 168

<211> 462

<212> DNA

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<213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (462)
      <223> n = A, T, C or G
      <400> 168
ggcacgaggn nnaacctncg gggctggggc aqcacqcctt qnqcaancct qcactqcact
                                                                        60
gaagacccgg tgccggaagc cgnnggcngc nacatqcagn aactqaacca qctqqqcqcq
                                                                       120
cancagttet cagacetgae agaggtgett ttacaettee taaetgatee anantangtg
                                                                       180
gaaatattnt tngttnatnt catntgaatn atccancncc aatcatanca nntttnattn
                                                                       240
cctcataanc nttgagaana gennecttnt gnttneanan ggtgetntga anangagtet
                                                                       300
cacangcaan caggtccaag cggatttnnt aactntgggt cttantgang agaaagncac
                                                                       360
ttacttttct gaaancngga agcagaatgc tcccaccctt gctcgatggg ccatacqtca
                                                                       420
agactctgat gattaaccag ctttanatat ggacnggaaa tt
                                                                       462
      <210> 169
      <211> 460
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(460)
      <223> n = A,T,C or G
      <400> 169
ggcacgaggg acagcagacn agacagtcac agcagccttg acaaaacgtt cctggaactc
                                                                        60
aagntettnt nencaaagga ggacagagca nacagcagag accatggant etnectegge
                                                                       120
coctoccac agatggtgca teccetggca naggeteetg etcacageet caettetaac
                                                                       180
cttctggaac ccgcccacca ctgccaagct cactattgaa tccacgccgt tcaatqnntc
                                                                       240
ntaggggaag gaggngcttt ctactnttnc acaatctgan ccccttcttn tttggttact
                                                                       300
ancatggctc tncatgtnaa aatactggna tggntaacct gtcaaattta taggnantnt
                                                                      360
gctaattggg aaactneenn tngtetaeee caggggneee agatteetnn gttencataa
                                                                       420
cnattaattt aacccctaat gncaanccct tngttaaaga
                                                                       460
      <210> 170
      <211> 508
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(508)
      <223> n = A, T, C or G
      <400> 170
ggcacgaggg ggatttttag gtggtcnggt gtggtatcag gaataatgtg ggaggccaqa
                                                                       60
ttgaagtcca ggccaggaac aatggtaatt gtgggactta agaaagtgtg agtacagctg
                                                                      120
aatgagccgg ggagcagaaa gtatatgcgt caggtatgag gaagaaaata gattttggaa
                                                                      180
gttatgagaa atgtagagag tgagttgagc atagtttgtg attttgaggg cctctaacag
                                                                      240
tattaaagca geggeagegg etgeacacag acatgatgge taggetaaaa caggaaggte
                                                                      300
aagttgtttg gacagaaagg ctacagggtg cagtcctggc tcttgtgtaa gaattctgac
                                                                      360
cacactaacc atgcctagga aggaaaggag ttgttctttt gtaagggatt gaggtttggg
                                                                      420
```

```
agattaatcg gacacgatca gcagggagag cacctgtgtt tttatgagaa ttatgctgag
                                                                        480
ataggtaaca gatgaggatg aaatttgg
                                                                        508
      <210> 171
      <211> 507
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(507)
      \langle 223 \rangle n = A,T,C or G
      <400> 171
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ccagcccacc tacaacccga cgctgcctta ctaccagccc atcccgggcg ggctcaacgt
                                                                       120
gggaatgtct gtttacatcc aaggagtggc cagcgagcac atgaagcggt tcttcgtgaa
                                                                       180
ctttgtggtt gggcaggatc cgggctcaga cgtcgccttc cacttcaatc cgcggtttga
                                                                       240
cggctgggac aaggtggtct tcaacacgtt gcagggcggg aagtggggca gcgaggagag
                                                                       300
gaagaggagc atgcccttca aaaagggtgc cgcctttgag ctggtcttca tagtcctggc
                                                                       360
tgagcactac aaggtggtgg taaatggaaa tcccttctat gagtacgggc accggcttcc
                                                                       420
cctacagatg gtcacccacc tgcaagtgga tggggatctg caacttcaat caatcaactt
                                                                       480
catcggaggc cagcccctcc ggcccca
                                                                       507
      <210> 172
      <211> 409
      <212> DNA
      <213> Homo sapien
      <400> 172
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cgatgactct gtgggagtgg aagtgtccag cgacagcttc tgggaggttg ggaactacaa
                                                                       120
acggactgtg aagcggattg acgatggcca ccgcctgtgt ggtgacctca tgaactgtct
                                                                       180
gcatgagcgg gcacgcatcg agaaggcgta tgcacagcag ctcactgagt gggcccgacg
                                                                       240
ctggaggcag ctggtagaga agggaccaca gtatgggacc gtggagaagg cctggatagc
                                                                       300
tgtcatgtct gaagcagaga gggtgagtga actgcacctg gaagtgaagg catcactgat
                                                                       360
gaatgaagac tttgagaaga tcaagaactg gcagaaggaa gcctttcac
                                                                       409
      <210> 173
      <211> 409
      <212> DNA
      <213> Homo sapien
      <400> 173
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                                                                        60
gtcagctcgc catgactgtg acctgctgcg ggaacagtat gaagaggagc aggaagccaa
                                                                       120
ggctgagctg cagagggcca tgtccaaggc caacagcgag gtagcccagt ggaggacgaa
                                                                       180
atatgagacg gatgccatcc agcgcacaga ggagctggaa gaggccaaga agaagctggc
                                                                       240
tragcgtctg caggatgctg aggaacatgt agaagctgtg aattccaaat gcgcttctct
                                                                       300
tgaaaagacg aagcagcgac ttcagaatga agtggaggac ctcatgattg acgtggagag
                                                                       360
gtctaatgct gcctgcgctg cgcttgataa gaagcagagg aactttgac
                                                                       409
      <210> 174
      <211> 407
      <212> DNA
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<213> Homo sapien

<400> 174				
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gtacggcggc aggggcgctc tggg	jttctcg atgcgtgcag	gcttttcggg	cccgcaactg	180
gtgggttgcc agcgttgatg tggt	ggagaa tgaagaggcc	agcgctagca	tcattqttaa	240
aatgacagac tcgttcactg agca	aggetga ceaggtgact	gctgaggttg	gaaagctctt	300
gggtgaagag aaggtggatg caat	tctttg cgttgctgga	ggatgggccg	ggggcaatgc	360
caaatccaag tctctcttta agaa	ctgtga cctgatgtgg	aaqcaqa	3333	407
<210> 175			•	
<211> 407				
<212> DNA				
<213> Homo sapien				
<400> 175				
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ctcttcgtgc ggctgctggc tctc	gccctg gctctggccc	tgggccccqc	cqcqaccctq	120
gcgggtcccg ccaagtcgcc ctac	cagetg gtgetgeage	acagcagget	ccadaaccac	180
cagcacggcc ccaacgtgtg tgct	gtgcag aaggttattq	gcactaatag	gaagtacttc	240
accaactgca agcagtggta ccaa	aggaaa atctqtqqca	aatcaacagt	Catcagctac	300
gagtgctgtc ctggatatga aaag	gtccct qqqqaqaaqq	gctgtccagc	ageceracea	360
ctctcaaacc tttacgagac cctg	ggagtc gttggatcca	ccaccac	-5	407
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<211> 409				
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<213> Homo sapien				
<400> 176				
ggcacgagtg gtgccaaaac ggga	ccatgc cctcctggag	gagcagagca	agcagcagtc	60
caacgagcac ctgcgccgcc agtt	cgccag ccaggccaat	gttgtggggc	cctggatcca	120
gaccaagatg gaggagatcg ggcg	catctc cattgagatg	aacgggaccc	tggaggacca	180
gctgagccac ctgaagcagt atga	acgcag catcgtggac	tacaagccca	acctggacct	240
gctggagcag cagcaccagc tcat	ccagga ggccctcatc	ttcgacaaca	agcacaccaa	300
ctataccatg gagcacatcc gcgt	gggctg ggagcagctg	ctcaccacca	ttqcccqcac	360
catcaacgag gtggagaacc agat	cctcac ccgcgacgcc	aagggcatc	JJ	409
<210> 177				
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<212> DNA				
<213> Homo sapien				
<400> 177				
ggcacgaggt ccaggtaact gcaa	aaacaa tggctcagca	tgaagaactg	atgaaqaaaa	60
ctgaaacaat gaatgtagtt atgg	agacca ataaaatgct	aagagaagag	aaggagcagg	120
tttcaaaaat ggcatcagtc cgtc	agcatt tggaagaaac	aacacagaaa	gcagaatcac	180
agttgttgga gtgtaaagca tctt	gggagg aaagagagag	aatgttaaaq	gatgaagttt	240
ccaaatgtgt atgtcgctgt gaag	atctgg agaaacaaaa	cagattactt	catgatcaga	300
tcgaaaaatt aagtgacaag gtcg	ttgcct ctgtgaagga	aggtqtacaa	qqtccactga	360
atgtatetet cagtgaagaa ggaa	aatctc aagaacaaat	tttqqaaa	JJ	408
	3	J.J		100
<210> 178				

<210> 178 <211> 92

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      <213> Homo sapien
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acaaaaaagt taaagagcta gaagaggaga tg
                                                                        92
      <210> 179
      <211> 411
      <212> DNA
      <213> Homo sapien
      <400> 179
ggcacgagga gacacgccac ctataccaca gttctcagaa tgaattagct aagttggaat
                                                                       60
cagaacttaa gagtctcaaa gaccagttga ctgatttaag taactcttta gaaaaatgta
                                                                       120
aggaacaaaa aggaaacttg gaagggatca taaggcagca agaggctgat attcaaaatt
                                                                       180
ctaagttcag ttatgaacaa ctggagactg atcttcaggc ctccagagaa ctgaccagta
                                                                       240
ggctgcatga agaaataaat atgaaagagc aaaagattat aagcctgctt tctggcaagg
                                                                       300
aagaggcaat ccaagtagct attgctgaac tgcgtcagca acatgataaa gaaattaaag
                                                                       360
agctggaaaa cctgctgtcc caggaggaag aggagaatat tgttttagaa g
                                                                       411
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      <211> 411
      <212> DNA
      <213> Homo sapien
      <400> 180
ggcacgaggt tgttcggagc gggcgagcgg agttagcagg gctttactgc agagcgcgcc
                                                                       60
gggcactcca gcgaccgtgg ggatcagcgt aggtgagctg tggccttttg cgaggtgctg
                                                                      120
cagccatage taegtgegtt egetaegagg attgagegte tecaeccate ttetgtgett
                                                                      180
caccatctac ataatgaatc ccagtatgaa gcagaaacaa gaagaaatca aagagaatat
                                                                      240
aaagactagt totgtoccaa gaagaactot gaagatgatt cagoottotg catotggato
                                                                      300
tettgttgga agagaaaatg agetgteege aggettgtee aaaaggaaac ateggaatga
                                                                      360
ccacttaaca tctacaactt ccagccctgg ggttattgtc ccagaatcta g
                                                                      411
      <210> 181
      <211> 411
      <212> DNA
      <213> Homo sapien
      <400> 181
ggcacgaggc gggacagggc gaagcggcct gcgcccacgg agcgcgcgac actgcccgga
                                                                       60
agggaccgcc accettgccc cctcagetgc ccactcgtga tttccagegg cctccgegeg
                                                                      120
cgcacgatgc cctcggccac cagccacagc gggagcggca gcaagtcgtc cggaccgcca
                                                                      180
ccgccgtcgg gttcctccgg gagtgaggcg gccgcgggag ccggggccgc cgcgccggct
                                                                      240
tctcagcacc ccgcaaccgg caccggcgct gtccagaccg aggccatgaa gcagattctc
                                                                      300
ggggtgatcg acaagaaact tcggaacctg gagaagaaaa agggtaagct tgatgattac
                                                                      360
caggaacgaa tgaacaaagg ggaaaggctt aatcaagatc agctggatgc c
                                                                      411
      <210> 182
     <211> 411
     <212> DNA
     <213> Homo sapien
     <400> 182
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ggcacgagcc gacatggagc tgttcctcgc gggccgccgg gtgctggtca ccggggcagg
                                                                        60
caaaggtata gggcgcgca cggtccaggc gctgcacgcg acgggcqcqc qqqtqqtqqc
                                                                       120
tgtgagccgg actcaggcgg atcttgacag ccttgtccgc gagtgcccgg ggatagaacc
                                                                       180
cgtgtgcgtg gacctgggtg actgggaggc caccgagcgg gcgctgggca gcgtgggccc
                                                                       240
cgtggacctg ctggtgaaca acgccgctgt cgccctgctg cagcccttcc tggaggtcac
                                                                       300
caaggaggcc tttgacagat cctttgaggt gaacctgcgt gcggtcatcc aggtgtcgca
                                                                       360
gattgtggcc aggggcttaa tagcccgggg agtcccaggg gccatcgtga a
                                                                       411
      <210> 183
      <211> 409
      <212> DNA
      <213> Homo sapien
      <400> 183
ggcacgagcc tacactctgg ccagagatac cacagtcaaa cctggagcca aaaaggacac
                                                                        60
aaaggactet egacecaaac tgeeceagae eeteteeaga ggttggggtg accaacteat
                                                                       120
ctggactcag acatatgaag aagctctata taaatccaag acaagcaaca aacccttgat
                                                                       180
gattattcat cacttggatg agtgcccaca cagtcaagct ttaaagaaag tgtttgctga
                                                                       240
aaataaagaa atccagaaat tggcagagca gtttgtcctc ctcaatctgg tttatgaaac
                                                                       300
aactgacaaa cacctttctc ctgatggcca gtatgtcccc aggattatgt ttgttgaccc
                                                                       360
atctctgaca gttagagccg atatcactgg aagatattca aatcgtctc
                                                                       409
      <210> 184
      <211> 410
      <212> DNA
      <213> Homo sapien
      <400> 184
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                                                                       60
caagcttgga ttgcccaaag agaagcttca ggacagcaaa gcatggtaga acaaccacca
                                                                       120
ggaatgatgc caaatggaca agatatgtct acaatggaat ctggtccaaa caatcatggg
                                                                       180
aatttccaag gggattcaaa cttcaacaga atgtggcaac cagaatgggg aatgcatcag
                                                                      240
caacccccac accccctcc agatcagcca tggatgccac caacaccagg cccaatggac
                                                                      300
attgttcctc cttctgaaga cagcaacagt caggacagtg gggaatttgc ccctgacaac
                                                                      360
aggcatatat ttaaccagaa caatcacaac tttggtggac cacccgataa
                                                                       41.0
      <210> 185
      <211> 411
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(411)
      <223> n = A, T, C or G
      <400> 185
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                                                                       60
agggtccacg gccaccatgg cgtattaggg gcagcagtgc ctgcggcagc attggccttt
                                                                      120
gcagcggcgg cagcagcacc aggctctgca gcggcaaccc ccagcggctt aagccatggc
                                                                      180
gcttctcacg gcattcagca gcagcgttgc tgtaaccgac aaagacacct tcgaattaag
                                                                      240
cacatteete gatteeagea aageacegea acatgacega aatgagette etgageageg
                                                                      300
aggtgttggt gggggacttg atgtccccct tcgacccgtc gggtttgggg gctgaagaaa
                                                                      360
gcctangtct cttagatgat tacctggagg tggccaagca cttcaaacct c
                                                                      411
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```
<210> 186
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      <212> DNA
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      <400> 186
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gcagcaatgg taccgcgagc accgctccga gctgaacctg cgccgcctct tcgatgccaa
                                                                      120
caaggaccgc ttcaaccact tcagcttgac cctcaacacc aaccatgggc atatcctggt
                                                                      180
ggattactcc aagaacctgg tgacggagga cgtgatgcgg atgctggtgg acttggccaa
                                                                      240
gtccaggggc gtggaggccg cccgggagcg gatgttcaat ggtgagaaga tcaactacac
                                                                      300
cgagggtcga gccgtgctgc acgtggctct gcggaaccgg tcaaacacac ccatcctggt
                                                                      360
agacggcaag gatgtgatgc cagaggtcaa caaggttctg gacaagatga
                                                                      410
      <210> 187
      <211> 506
      <212> DNA
      <213> Homo sapien
      <400> 187
ctttcgtggc tcactccctt tcctctgctg ccgctcggtc acgcttgtgc ccgaaggagg
                                                                       60
aaacagtgac agacctggag actgcagttc tctatccttc acacagctct ttcaccatgc
                                                                      120
ctggatcact tcctttgaat gcagaagctt gctggccaaa agatgtggga attgttgccc
                                                                      180
ttgagatcta ttttccttct caatatgttg atcaagcaga gttggaaaaa tatgatggtg
                                                                      240
tagatgctgg aaagtatacc attggcttgg gccaggccaa gatgggcttc tgcacagata
                                                                      300
gagaagatat taactctctt tgcatgactg tggttcagaa tcttatggag agaaataacc
                                                                      360
tttcctatga ttgcattggg cggctggaag ttggaacaga gacaatcatc gacaaatcaa
                                                                      420
agtctgtgaa gactaatttg atgcagctgt ttgaagagtc tgggaataca gatatagaag
                                                                      480
gaatcgacac aactaatgca tgctat
                                                                      506
      <210> 188
      <211> 506
      <212> DNA
      <213> Homo sapien
      <400> 188
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                                                                      120
atgggaccgt tctcagctcc agtggaacca ggtttgctgt gaactttcag actggcttca
                                                                      180
gtggaaatga cattgccttc cacttcaacc ctcgytttga agatggaggg tacgtggtgt
                                                                      240
gcaacacgag gcagaacgga agctgggggc ccgaggagag gaagacacac atgcctttcc
                                                                      300
agaaggggat gecetttgae etetgettee tggtgeagag eteagattte aaggtgatgg
                                                                      360
tgaacgggat cetettegtg cagtaettee acegegtgee ettecacegt gtggacacea
                                                                      420
teteegteaa tggetetgtg cagetgteet acateagett ceageeteee ggegtgtgge
                                                                      480
ctgccaaccc ggctcccatt acccag
                                                                      506
      <210> 189
      <211> 399
      <212> DNA
      <213> Homo sapien
      <400> 189
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                                                                      60
ctggagcccc agaggatgaa agatcgcaga gcacagcccc ccaggcacca gagtgcttcg
                                                                     120
accetgeegg accggetggg etegtgagge egacatetgg cettteecag ggeecaggaa
                                                                     180
```

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300

360

420 480

503

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	Lvs	Glu	Glu	_	Val	Thr	Asp	Leu		Thr	Ala	Val	Leu	Tyr	Pro
	-4		20					25					30	-1-	
Ser	His	Ser	Ser	Phe	Thr	Met	Pro	Gly	Ser	Leu	Pro	Leu	Asn	Ala	Glu
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Ala	Cys	Trp	Pro	Lys	Asp	Val	Gly	Ile	Val	Ala	Leu	Glu	Ile	Tyr	Phe
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	Ser	Gln	Tyr	Val		Gln	Ala	Glu			Lys	Tyr	Asp	Gly	
65	21-	C 1	1	Th ess	70	Tla	~1	7		.75	33-	T	M	a 1	80 Db
Asp	AId	GIY	гуя	85	1111	116	GIY	теп	90 91	GIII	Ala	ьуs	мес	Gly 95	Pne
Cvs	Thr	Asn	Ara		Asp	Tle	Asn	Ser		Cvs	Met	Thr	٧al	Val	Gln
C, D	****	1100	100	010	715p	110	21011	105	DC u	Cys	ric, c	****	110	VUI	GIII
Asn	Leu	Met		Arg	Asn	Asn	Leu		Tyr	Asp	Cys	Ile		Arg	Leu
		115		_			120		_	•	•	125	- 1		
Glu	Val	Gly	Thr	Glu	Thr	Ile	Ile	Asp	Lys	Ser	Lys	Ser	Val	Lys	Thr
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Len	Sar	Dro	λla	5 Val	Pro	Dhe	Sor	Clv	10 Thr	Tla	Gl n	Gly	Glv.	15	Cln
Ten	DET	FIU	20	Val	£10	LHE	SET	25	TIIT	116	GIII	grð	30	Leu	GIII
Asp	Glv	Leu		I)e	Thr	Val	Asn		Thr	٧al	Len	Ser		Ser	Glv
	1	35					40	1				45			1
Thr	Arg		Ala	Val	Asn	Phe		Thr	Gly	Phe	Ser		Asn	Asp	Ile
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Ala	Phe	His	Phe	Asn	Pro	Arg	Phe	Glu	Asp	Gly	Gly	Tyr	Val	Val	Cys
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Asn	Thr	Arg	Gln		Gly	Ser	Trp	Gly		Glu	Glu	Arg	Lys	Thr	His
Mot	D	DF -	O1-	85	03	Met	D	nl	90	*	~	DI :	.	95 375 3	61

Met Pro Phe Gln Lys Gly Met Pro Phe Asp Leu Cys Phe Leu Val Gln

Ser Ser Asp Phe Lys Val Met Val Asn Gly Ile Leu Phe Val Gln Tyr 120 Phe His Arg Val Pro Phe His Arg Val Asp Thr Ile Ser Val Asn Gly

135 140

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Arg Pro Thr Ser Gly Leu Ser Gln Gly Pro Gly Lys Glu Thr Leu Glu 55

Ser Ala Leu Ile Ala Leu Asp Ser Glu Lys Pro Lys Lys Leu Arg Phe 70

His Pro Lys Gln Leu Tyr Phe Ser Ala Arg Gln Gly Glu Leu Gln Lys 90

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Val Asp Ile Cys 130

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His Ile Leu Cys Thr Gly Asn Leu Cys Thr Lys Glu Ser Tyr Asp Tyr 40

Leu Lys Thr Leu Ala Gly Asp Val His Ile Val Arg Gly Asp Phe Asp 55

Glu Asn Leu Asn Tyr Pro Glu Gln Lys Val Val Thr Val Gly Gln Phe 75

Lys Ile Gly Leu Ile His Gly His Gln Val Ile Pro Trp Gly Asp Met 90

Ala Ser Leu Ala Leu Leu Gln Arg Gln Phe Asp Val Asp Ile Leu Ile 105

Ser Gly His Thr His Lys Phe Glu

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64

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115 120

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40 Ser Gly Ala Lys Pro Tyr Ser Cys Asn Phe Cys Glu Lys Ser Phe Arg

55 Gln Leu Ser His Leu Gln Gln His Thr Arg Ile His Thr Gly Asp Arg

70

Pro Tyr Lys Cys Ala His Pro Gly Cys Glu Lys Ala Phe Thr Gln Leu

Ser Asn Leu Gln Ser His Arg Arg Gln His Asn Lys Asp Lys Pro Phe 105 110

Lys Cys His Asn Cys His Arg Ala Tyr Thr Asp Ala Ala Ser Leu Glu 120

Val His Leu Ser Thr His Thr 130

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Gln Asp Val Pro Gly Pro Ala Ser Ser Gly Ala Ala Ala Ala Ser Ala 40

His Ala Ala Asp Trp Asn Lys Tyr Asp Asp Arg Leu Met Lys Ala Ala

Glu Arg Gly Asp Val Glu Lys Val Thr Ser Ile Leu Ala Lys Lys Gly 75

Val Asn Pro Gly Lys Leu Asp Val Glu Gly Arg Ser Val Phe His Val 90

Val Thr Ser Lys Gly Asn Leu Glu Cys Leu Asn Ala Ile Leu Ile His 105

Gly Val Asp Ile Thr Thr Ser Asp Thr Ala Gly Arg Asn Ala Leu His 120

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65

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tgccatttgt	ggggggtgca	accacaacat	aagtcagaaa	aaaagctatc	cagcttttcg	180
tggaatctgg	tgaagtttac	acttagcgat	aagcctctaa	gcctgaactt	agcagggcta	240
gcaaaacttt	atttatttcc	taactcctat	tattttagaa	tggttttcaa	aataatactg	300
caagttccta	attgaaatac	aaaacagaac	aaaaagctgt	gagaaatctt	tttttttctt	360
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tttgatgtac	ttgctcttga	aagcactaga	acaaattaat	tgaaataaaa	cctctctgaa	480
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                                                                    180
ttataccacg gactgctata cagccaaagc cagtctgqct qqaactctct ctctqatqct
                                                                    240
gatttgcact ctgctggaat tctgcctagc tgtgctcact gctgtgctgc ggtggaaaca
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ggcttactct gacttccctg ggagtgtact tttcctgcct cacagttaca ttggtaattc
                                                                    360
tggcatgtcc tcaaaaatga ctcatgactg tggatatgaa gaactattga cttcttaaqa
                                                                    420
aaaaagggag aaatattaat cagaaagttg attcttatga taatatggaa aagttaacca
                                                                    480
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120 .
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                                                                    180
tcccaaacat cttatgaaaa agtatacaac tctacttcaa aatatgctat ttactcactg
                                                                    240
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                                                                    120
tatggttcag gcgcacttca catgtgcaaa gatggagaaa gcactcacct acacgtttag
                                                                    180
gctcagaatg ttgattgaaa cattttgaat gatcaaaaat aaaatgttat tttt
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aaacaataca caaataaaaa ttatgaggtt acgaatacac atccagtttc gaatccaatt
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tctttt
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                                                                       120
caataaacct aattatggaa cagaaatttg cattctgttt ccagtgctac tacactccta
                                                                       180
ctttctcaaa agtctgctct attaatatca gctcagtgca gtttactatg aatagtttat
                                                                       240
gtctgtgatg caaagcatta attgttctct ttttacaaac atacatttt ttcataagga
                                                                       300
agactggggg aaaacccaga aacatacaga gaaaaggaaa gcatcatcaa atatatgtta
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gtttctgacg tagaagagct tacccctcca gagcatcttt ctgatcttcc accattttca
                                                                       180
aggtgtttaa taggaataat aataaagtct tcgaatgtgg tcaggtcatt tttggatgaa
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ttaaaggcat gtgtggcttc taatgatatt gaaggcattg tgtgcctcac ggctgctgtg
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cctggactat tgaaatcaag cttattggat taagtgatat ttctatagcg attgaaaggg
                                                                      180
caatagttaa agtaatgagc atgatgagag tttctgttaa tcatgtatta aaactgattt
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tragettrae aaatatgrea gtttgeagtt atgeagaate caaagtaaat gteetgerag
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gacaatgtta gtgaactcaa					240
gaaacccttt gaggtccaat	tttcacatca	tattctccaa	atagtaaaat	agcagctcta	300
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0.0					
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aagccacatc atttaatttt	gtatctaaaa	tttatttggg	gtcttatatg	ttatttctca	180
tgtaaccctt attaggactc	attttagccc	taaattacct	gtggctgttt	ctttttattt	240.
ttttgactac ttttatatta		-	_		300
ttggatagcc tggatacttt	gttagatgag	tatttagctg	tgtctgcaaa	tcttaaaagc	360
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gcctcaagca gagacaaagg aggaagttgc ctatgttgta tqqtttacaq qccataaatq
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ctctgtggaa gatattcaaa agccacaagt ggtgcaaatg tttatggttt ttatttttca
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489

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acaatagaaa actaacaaat gagcaacaat ataaagagta gaggtagttc tcattgggtg
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tgggtccata aggaaaaact gtagtagaaa tggttaggac aaacaataaa gtagaaacag
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gggggaaact tgagaagaga agaaagaagc aagaaaaaaa gactttcaat tgtataaaat
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tcacaaacca gtaaagtata aagacaccat ggagaaatgg ttaactctgc cccaaacacc
                                                                       300 -
caacagcaaa caaaaccaga atgaataagc ctttggcaga caattttaga aatttgaatq
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ttacatttct caataattca caaacaatat attatatggt atatttatat taaatattgg
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gaaaccaatg tigtaaatti gatgcttata atgctttagc caatgagagc acaatgatat
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caatcaagct aaatgaatgc tggtgttatc acaacagtgc tcatttatga aacaa
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      <212> DNA
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                                                                      180 .
agactgtctg gaaggcttgg aatggtttat tgcttatggt aaaatttgcc tgatttctta
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caggcagcgt ttggaaacct tttattatat agttgtttac atacttataa gtctatcatt
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tagggagaaa atgcaaatgt ctcaattttt gttcacaaaa gtatatttta tcaaattgct
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tatagattac tatggaacca gacttacaag actgagtatt actaatgaaa catttagaaa aacgcaatta tatccataaa tattttt	480 508
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acactcatgg atatgtaaaa actgtcaaga ttaaaaattta atagtttcat ttatttgtta
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ttttatttgt aagaaatagt gatgaacaaa gatccttttt catactgata cctqqttqta
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tattatttga tgcaacagtt ttctgaaatg atatttcaaa ttgcatcaag aaattaaaat
catctatctg agtagtcaaa atacaagtaa aggagagcaa ataaacaaca tttggaaaaa
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aaaaaaaaaa aaaa
                                                                        374
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gtctttgtgt tatgatcaat gaagaagggc cggccgtttg gcgctatcct catttcccag
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ccgggtggca agaagctctg tgtgactttg tgttgtggtt tgggggagtt gtaaggtgat
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atattaaaaa ggaaactaat tggaccattt tctatttgtc tattttatac aaaaaggcta
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cacaattgat acactctatt cagataacaa tcaattagag tgantatgaa ttactggcga
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caccatcact caattcttaa aaattagaaa ttgctgtagc agtattcact ataacttaac
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totgatttat coaatotttt tattatacat ttatottttg togttatata ctggtgtgtg
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atccaagtta tacatgaata gaaaaagatg gtgttaaatt tgtgtgtagg ctgggaattc
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tngctaaagg aatggnaaaa aacctgtnnt tgnaaaattn acntgtccca aagnnaagga
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ttccatagtg ccaattatca aaggccttga ctacttagca ttgctgtatt acagatgtgc
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acactetgae acatgetetg agaatactgg gaetgetgtt teaaaaaaaa aggtteaaac
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ttcacatcaa gagtacccca agaaaaacga aatccatggc acanacactg tacaagggtg
                                                                       360
cagggcaggg ctctgagggg cccaaacccc attttgccaa ctcgattttc tagcattgaa
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aattgatttc attcttattt caatgcagat tgttggacct tcagatggaa gtagttacat
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tggctacaca ctctcactac acacacagac cccacagtcc tatatgccac aaacacattt
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ccataacttg aaaatgagta ttttgcatat ctcagttcag gatatgtttt ttacaagtta
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tacageteet attgatagga catagtggaa gtgagetaca acgtagtacg tgtegtgtag
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tgtggcgagt cagctaaata ctttgacgcc ggtggggata gcgatgatta tggtagcgga
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ggtgaaatat gctcgtgtgt ctacgtctat tcctactgta aatatatggt gtgctcacac
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gataaaccct aggaagccaa ttgatatcat agctcagacc atacctatgt atccaaatgg
                                                                      480
ttcttttttt ccggagtagt aagttacaat atgggagatt attccgaagc ctggtaggat
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aagaatataa acttcagggt gaccgaaaaa tcagaatagg tgttggtata gaatggggtc
                                                                      600
tectneteeg eggggtenaa gaaggtggtg ttgangttge eggnetgtta ntagtatagn
                                                                      660
gatgccanca gct
                                                                      673
```

```
<210> 248
      <211> 149
      <212> DNA
      <213> Homo sapien
      <400> 248
cctcttcatt gttcacatgt cacaggagga ggctctgagc aaaggccact ggcaagttag
                                                                       60
ggcaacacca agaaggctct gcggagagac tccctgtggg ttggggcctg gcaggaacgg
                                                                      120
tgcctgtgga ctgtttatgg tctgtccag
                                                                      149
      <210> 249
      <211> 458
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(458)
      \langle 223 \rangle n = A,T,C or G
      <400> 249
gaagctaaat ccaaagaaat atgaaggtgg ccgtgaatta agtgatttta ttagctatct
                                                                      60
acaaagagaa gctacaaacc cccctgtaat tcaagaagaa aaacccaaga agaagaagaa
                                                                      120
ggcacaggag gatctctaaa gcagtagcca aacaccactt tgtaaaagga ctcttccatc
                                                                      180
agagatggga aaaccattgg ggaggadtag gacccatatg ggaattatta cctctcaggg
                                                                      240
ccgagaggac agaatggata taatctgaat cctgttaaat tttctctaaa ctgtttctta
                                                                      300
gctgcactgt ttatggaaat accaggacca gtttatgttt gtggttttgg gaaaaattat
                                                                      360
ttgtgttggg ggaaatgttg tgggggtggg gttgagttgg gggtattttc taatttttt
                                                                      420
tgtacatttg gaacagtgac aataaatgan accccttt
                                                                      458
      <210> 250
      <211> 374
      <212> DNA
      <213> Homo sapien
      <400> 250
aaaaaacaaa acaatgtaag taaaggatat ttctgaatct taaaattcat cccatgtgtg
                                                                       60
atcataaact cataaaaata attttaagat gccggaaaag gatactttga ttaaataaaa
                                                                      120
acactcatgg atatgtaaaa actgtcaaga ttaaaaattta atagtttcat ttatttgtta
                                                                      180
ttttatttgt aagaaatagt gatgaacaaa gatccttttt catactgata cctggttgta
                                                                      240
tattatttga tgcaacagtt ttctgaaatg atatttcaaa ttgcatcaag aaattaaaat
                                                                      300
catctatctg agtagtcaaa atacaagtaa aggagagcaa ataaacaaca tttggaaaaa
                                                                      360
aaaaaaaaa aaaa
                                                                      374
     <210> 251
     <211> 356
     <212> DNA
     <213> Homo sapien
      <400> 251
aaagatcttc tctaacaagc tatgggaatt tggcttcata ctctttcttt gcaacagcag
                                                                       60
tgttctgggt gataattttg aattgatacc tgttcctttt tctgggtttt gttggctttt
                                                                      120
tgaaaaattg tctttcctta tcattggtgg gaggcttggt agcaaagtaa catttttgg
                                                                      180
aaaagaggac agaaaaattg aactacagct tgagaacgta ttctttttt cctactttgt
                                                                      240
tattgcaaat tgaggaatca cttttaactg ttttaggtgt gtgtgtccag agtgagcaag
                                                                      300
```

gattatgttt ttggattgtc aaaga	ggatg cttagtctta	aaataaaaat	aaattt	356
<210> 252				
<211> 484				
<212> DNA				
<213> Homo sapien	·			
<400> 252				
ctggtaaact gtccaaaaca aggtt	ccaaa taacacctct	tactgattta	ccctacccat	60
acatatccca aatagttttt gatca	aaaac atgaaataga	tccacctgct	tattttaagc	120
atattaaaaa ggaaactaat tggac	cattt tctatttgtc	tattttatac	aaaaaggcta	180
cacaattgtt acactttatt cagatt	tacaa ttaattagag	tgattatgaa	ttagtgttct	240
acaccattac tcaattctta aaaatt	tagaa attgctgtag	cagtattcac	tataacttaa	300
cactacgaga gacttaaaaa acagt	tactg caaaaaaaaa	aaagagctac	ttcaaagcaa	360
gcaaagtcag taccattaca gatat	ctta aaaaaaaaaa	aaaatttaac	aagcaaggct	420
agggtttgat aaattccatc ttgtg	atcca ttcttgtgca	ttcttcactt	cttgagtcac	480
tece				484
<210> 253				
<211> 379				
<212> DNA				
<213> Homo sapien				
<400> 253	•			
aaaaagcgct tagacttccc tttcca	atctq qaacatqtaa	aattttgcag	caacaggttt	60
totocaatic ottoagcaag aatto	cago ctacacacaa	atttaacacc	atctrttct	120
attcatgtat aacttggatc acacac	cagt atataacqac	aaaagat.aaa	tgtataataa	180
aaagattgga taaatcagaa gaggct	tttt ggtcttgaat	tcttcaccca	ctaacaatga	240
agcagcactg taggcagccc aaaaca	acacc aaacagtttt	ataagtgtag	acaccacttc	300
aaatgatcca accaccaaaa gtacag	gggc tattacaatg	agaggaagta	atgaatatcc	360
tataactcca aggacttgg				379
<210> 254				
<211> 387				
<212> DNA				
<213> Homo sapien				
<220>	•			
<221> misc_feature				
<222> (1)(387)				
<223> n = A,T,C or G				
<400> 254				
aaatttgact tttcagtgcc tcagtt	tgca catctgtaat	acagcaatgc	taagtagtca	60
aggccnttga taattggcac tatgga	aatc ctgcaagatc	ccactacata	tgtgtggagc	120
agaagggtaa ctcggctaca gtaaca	gctt aattttgtta	aatttgttct	ttatactgga	180
gccatgaagc tcagagcatt agctga	ccct tgaactattc	aaatgggcac	attagctagt	240
ataacagact tacataggtg ggccta	aagc aagctcctta	actgagcaaa	atttggggct	300
tatgagaatg aaagggtgtg aaattg	acta acagacaaat	catacatctc	agtttctcaa	360
ttctcatgta aatcagagaa tgcctt	t			387
<210> 255	•			
<211> 225				
<212> DNA				
<213> Homo sapien				

```
<220>
      <221> misc_feature
      <222> (1)...(225)
      <223> n = A,T,C or G
      <400> 255
aaatgtcttg tttcccagat ttcaggaaan tttttttctt ttaagctatc cacagcttac
                                                                       60
agcacctttg ataaaatata cttttgtgaa caaaaattga gacatttaca ttttctccct
                                                                      120
atgtggtcgc tccagacttg ggaaactatt catgaatatt tatattgtat ggtaatatag
                                                                      180
ttattgcaca agttcaataa aaatctgctc tttgtatgac agaat
                                                                      225
      <210> 256
      <211> 544
      <212> DNA
     <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(544)
      <223> n = A,T,C or G
      <400> 256
ccttgcttaa agcccagaag tggtttaggc ntttggaaaa tctggttcac atcataaaga
                                                                       60
actigatiti aaatgiitti tatagaaaca agigctaagi gtaccgiati atactiqatq
                                                                      120
ttggtcattt ctcagtccta tttctcagtt ctattatttt agaacctagt cagttcttta
                                                                      180
agattataac tggtcctaca ttaaaataat gcttctcgat gtcagatttt acctgtttgc
                                                                      240
tgctgagaac atctctgcct aatttaccaa agccagacct tcagttcaac atgcttcctt
                                                                      300
agetttteat agttgtetga cattteeatg aaaacaaagg aaccaacttt gttttaacca
                                                                      360
aactttgttt ggttacagtt ttcaggggag cgtttcttcc atgacacaca gcaacatccc
                                                                      420
aaagaaataa acaagtgtga caaanaaaaa aacaaaccta aatgctactg ttccaaagag
                                                                      480
caacttgatg gtttttttta atactgagtg caaaaggnca cccaaattcc tatgatgaaa
                                                                      540
tttt
                                                                      544
      <210> 257
      <211> 420
      <212> DNA
      <213> Homo sapien
      <400> 257
aaatgtcttg tttcccagat ttcaggaaac tttttttctt ttaagctatc cacagcttac
                                                                       60
agcaatttga taaaatatac ttttgtgaac aaaaattgag acatttacat tttctcccta
                                                                      120
tgtggtcgct ccagacttgg gaaactattc atgaatattt atattgtatg gtaatatagt
                                                                      180
tattgcacaa gttcaataaa aatctgctct ttgtatgaca gaatacattt gaaaacattg
                                                                      240
gttatattac caagactttg actagaatgt cgtatttgag gatataaacc cataggtaat
                                                                      300
aaacccacag gtactacaaa caaagtctga agtcagcctt ggtttggctt cctagtgtca
                                                                      360
attaaacttc taaaagttta atctgagatt ccttataaaa acttccagca aagcaacttt
                                                                      420
      <210> 258
      <211> 736
      <212> DNA
      <213> Homo sapien
      <400> 258
aaacaaaatg ctaaacctaa aaacattgtt ctgtcagttc ccaaattaaa tctacttaga
                                                                       60
```

<213> Homo sapien

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acaaaaacaa aaatttatag ctcggtcaca tactacttaa ataatattgt tcaggcatct
                                                                       120
ctaaaatcct ccatgttttc aagtatggaa atagaactca aatattccac aatacagtac
                                                                       180
taaacagatg gagtatttag gaaagacttt gttgtcatat ggcacaatat taatatttg
                                                                       240
ttgcttcaat acgttttgaa ataaatatca gatttttgtt ttttttcct aaaagaccaa
                                                                       300
aattataatc tacattaaga taattctgac tgtggttaag acttaagagt gtaaaataca
                                                                       360
acatcaatat tttatcacaa aagtaaagct ggtaacaaat tataaaagga gccagtactc
                                                                       420
tactgagaca ggctcggaga ttaaagctca tcatgataga aatagtcatc atggagctgt
                                                                       480
ctgccataat ctgtggcttc actggtgaga aacaagtccg ggttttccag aatctcttct
                                                                       540
tcagagagct ttttgtcacc attcaaatcc atttcatcaa ttagatgaag cgcctcctct
                                                                       600
tgtgcaatgc cctgattatt aggtctaccc aaggtaacag ctcttgggga tcaagcctgc
                                                                       660
catcgttatc tttgtcataa tcattcaccg aatctgtctt tctcacaagt atcccattct
                                                                       720
ggatcttcat ttgcag
                                                                       736
      <210> 259
      <211> 437
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(437)
      <223> n = A,T,C or G
      <400> 259
aaaaccatac tgaaatcatt taccaaataa cnaagatctt aatctaaaag atagtgaata
                                                                        60
catcatcatc atgaaatctg gttttatgtg ctctatgaag tacttggaga attgctttt
                                                                       120
tatttttctt ttgctttatt aggtcacaca aaacagaatg aattagcaga aaaatgtatg
                                                                       180
tratagaaca gcatttacta cttcaattta attttttta ctaacaattq tqqaccttt
                                                                       240
tgatgacact tatgtatgtt tttaataaat tatgtactta ttagtactta atgagccctt
                                                                       300
cotgoctcaa tataaaatta ctaaacttgg agaattacag attttattgt aggccctgat
                                                                      360
gttagtcact ttggagaagc taaaaatttg gaaatgatgt aattcccact gtaatagcat
                                                                       420
agggattttg gaagcag
                                                                      437
      <210> 260
      <211> 592
      <212> DNA
      <213> Homo sapien
      <400> 260
ttttttttt gaaaaatata aaattttaat aaaggctaca tctcttaatt acaataatta
                                                                       60
ttgtaccaag taattttcct taaatgaact ctttataatg cataatttac agtataagta
                                                                      120
gaacaaaatg tcatgacaaa agtcattgag tacaagactt gtaataaaaa ggcataaaat
                                                                      180
atatttatac ataaacccct ttcaaaaaac aagggaaagc ttgagccctc aatatagggc
                                                                      240
gacacacgga gcgggtgacc gtgcaggtac aggtactgta ctgatttaaa gtcaagcact
                                                                      300
agagatagtg gattaatact cttttgccgt acactatata cagatgtata gtacaagtaa
                                                                      360
caatggcaaa cagaatgtac agattaactt aacacaaaaa cccgaacatc aaaatgaagg
                                                                      420
tgtgtggagg aaaggtgctg ctgggtctcc ctacaactgt tcatttcttt gtggggcagg
                                                                      480
gggtagttcc tgaatggctg tggtccaatg actaatgtaa aacaaaaaca gaaacaaaaa
                                                                      540
aaacaaggaa ctgtcatttc cacgaaagca cagcggcagt gattctagca gg
                                                                      592
      <210> 261
      <211> 450
      <212> DNA
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```
<400> 261
gtggcagggc ccagccccga accagacaag ggacccctca aggagcttca ttctagcatg
                                                                       60
agaaaattga gaagtaaacc agaaagttac agaatgtctg aaggggacag tgtgggagaa
                                                                      120
tccgtccatg ggaaaccttc ggtggtgtac agatttttca caagacttgg acagatttat
                                                                      180
cagteetgge tagacaagte cacaceetae aeggetgtge gatgggtegt gacaetggge
                                                                      240
ctgagctttg tctacatgat tcgagtttac ctgctgcagg gttggtacat tgtgacctat
                                                                      300
gccttgggga tctaccatct aaatcttttc atagcttttc tttctcccaa aqtqqatcct
                                                                      360
tccttaatgg aagactcaga tgacggtcct tcgctaccca ccaaacagaa cgaggaattc
                                                                      420
cgccccttca ttcgaaggct cccagagttt
                                                                      450
      <210> 262
      <211> 239
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(239)
      <223> n = A, T, C or G
      <400> 262
taactttgat gacaaaatct aaaattaaag anttaqtctt aaaaqcctat aqtqacttgt
                                                                       60
ttacttgcat aaataatatt ttcacttagt acaggctatt aatataagta atgagaattt
                                                                      120
aagtattaac tcaaaaaaag atagaggctc caaacttttc taagaaatta atgcattttc
                                                                      180
aaagtaataa tataatcaat ctgtaagtca aaagtaattt catattcatt gccaaattt
                                                                      239
      <210> 263
      <211> 376
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(376)
      <223> n = A,T,C or G
      <400> 263
aaaaaaaaaa aaaaaaaatt ccttgtngtt tnttagagga aaaaaagaaa aaccccaact
                                                                       60
tttancactg atactacata ttgctctgtt aaagaatttt ctctgccaaa aaaaaqaaaa
                                                                      120
aacaaaaaaa cgcttaaagc tggagtttga cattctgctt tcagatgctg tctttttatt
                                                                      180
agtgagtgat gatggtttgc taataatcaa taggtaataa ttttttgtaa tcccatcaag
                                                                      240
tggctccata tgtttctgct ctctcgtgac tgtgttaatg tttaactgtt gtaccttaaa
                                                                      300
gccgaaatca gtaactatgc atactgtaac caaggtattg ggcttacaga gttgtttgtt
                                                                      360
gnataaagaa aatttt
                                                                      376
      <210> 264
      <211> 207
      <212> DNA
      <213> Homo sapien
      <400> 264
aaattagcat tccacaaata tacaggtaat ttaataatta ttgtgcatga atacatacac
                                                                       60
aatgcttata tatacaaatt ccagtttgtt ttcatgtgct ggcaagggat ttgtatacaa
                                                                      120
tcataagctg tgttcatatt ggtcccattg aatattcaca atacaaaagc acaaaagaac
                                                                      180
cattgattta caaaaggaaa tctattt
                                                                      207
```

```
<210> 265
      <211> 388
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(388)
      <223> n = A,T,C or G
      <400> 265
naactgcact ttatttgtta ctgtaacatt nttttttaac tgatcaacca taagcatgca
                                                                       60
aaagnccnct gaaactgctt ccactgcctg ttgtatagaa atgggtaaat tataaaggtg
                                                                       120
attcaatttg gagctccttc cttttttata gcacttctaa gctgtgtgcg cgacacacac
                                                                       180
cacagaggta ggaaggacca cctttaataa attatcttct taatcgcaga gaatttctga
                                                                       240
agataaaact gacaaaatgc taaaccaagg ctttgatgag tcccaaagga ccacagatcc
                                                                       300
atcggctcct atttgaagaa ttcatcccct gtagtgttct agcctttgta qqqcactqqa
                                                                       360
ttacaagatc caccagggct ctgaacaa
                                                                       388
      <210> 266
      <211> 616
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(616)
      <223> n = A,T,C or G
      <400> 266
aaatacagag tcaaaagatg atttataaaaa tntaaaaacat tttctgcttg gccgtatttg
                                                                       60
aagacaagct gaatacatat ctatgttctg aataagtcca ctatggatat atataggaag
                                                                      120
agatatacat atatccatcc acagatacac acacacatat atatttctgc atgtatatat
                                                                      180
acataattct ttctatagtt acaggaaata cttcttctat aattctgatt ttgactccca
                                                                      240
tectecacea titacteate caeteattae etaaatettg getitette etatatigta
                                                                      300
aataatccat ccaaacttct agccagtact gtcaggaggg ttcttgctcg agtgagctgt
                                                                      360
taatactatt ttccactgac aacttctgca catcgaggac acagtgtatc tgaagactcc
                                                                      420
gctgtatact tccaacaacg ggggcatttt tctttcgtag tcggcatgac aattacttta
                                                                      480
taggaagact cttcacgaat atcaccacct tctaagttga tgaggaattt ccctttaagc
                                                                      540
togattacat otgoagtcat ototogtggt tootgaccag taaagttgac toagaagcca
                                                                      600
tcattaattc attcaa
                                                                      616
      <210> 267
      <211> 341
      <212> DNA
      <213> Homo sapien
      <400> 267
ccattatgta tgtattttct tgaaaaatac ttatttcagc tacttatttt taatagttac
                                                                       60
ttattcttgt tgtattgtca tttgagtttt gtatatattt ttgatattaa ccccttgtca
                                                                      120
catgtataat ttgcaaatat tttctccctt tttttagttg tcacattctg ttcattgtat
                                                                      180
cagattctgt gcagcagctt tttaatttga agtgatctga ctgacttgtt cttccttttg
                                                                      240
tgtcctggga tatttaggtt aaatcaaaaa acttgctgcc cagaccaatg ttatggggct
                                                                      300
ttcactctat tttttggtag tagtagttta agagttttag g
                                                                      341
```

```
<210> 268
      <211> 367
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (367)
      <223> n = A,T,C or G
      <400> 268
ttgtagattg gaatagcaaa agtgaatgct ntgaccaaaa tttttgccct cctaaataaa
                                                                        60
gacgtntcct tctagagagc aaatctatca taaaatgtca aaactagaag agaataaaat
                                                                        120
gaaaggaaaa aacctagaaa aatatcctaa aatatcaaat gcagtcattt ctaaatataa
                                                                        180
gccataatta tagctttacc tattgttctt attgttccta tgctgcttct acaatgttac
                                                                        240
atcaactata cttagcttta ctctcccaaa atcttggtga tgaagccttc tgagtgtgct
                                                                        300
ttccaatgtg ccagaaccag aagggcattc caaggcttcc ccacatttcc tccatttacq
                                                                        360
gagacag
                                                                        367
      <210> 269
      <211> 270
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(270)
      \langle 223 \rangle n = A,T,C or G
      <400> 269
caaatctctc cctcactaga cgtaagccnt ttnctcactc tctcaatctt atgcatcata
                                                                        60
gnaangengn tgaggtggat taaaccaaac ccagetacge aaaatettag catacteete
                                                                        120
aattacccac ataggatgaa taataqcagt tctaccqtac aaccctaaca taaccattct
                                                                        180
taatttaact atttatatta tootaactac tacegcatee etactactea aettaaacte
                                                                        240
cagcaccacg accctactac tatntcgcac
                                                                        270
      <210> 270
      <211> 368
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(368)
      <223> n = A,T,C or G
      <400> 270
ctgaatcatg aataacacta tataatagag tntaaggaac acaagcatta gatgtgatcc
                                                                         60
ttgccccata cccttagatt atgtcagact aaagctgaca attctgccag gctctgaacc
                                                                        120
cctagtgccc ccaacccaaa tcttggaagc aaagaatatg ccctgtcata caactttgta
                                                                        180
caagttgtag taaaacaaag cttaagtttt ctcatctttc tacagcaaat ggtcagttat
                                                                       240
ttaataaaca ctaaaatgct cctaagaatc cattttgagt ttgtttacca aacacattgt
                                                                        300
gcaagaactg actacacaaa aagttccttt gaaatttggt ccacaaattc acttaaggtt
                                                                        360
ggaaattt
                                                                        368
```

```
<210> 271
      <211> 313
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(313)
      <223> n = A, T, C or G
      <400> 271
aaatttatat aaaactctgt acatgttcac tttattattg cataaacagc ataatcttca
                                                                         60 ·
agacaanngt ttgcaaacac atgtccaatt caggaaaaaa aatttcacgt ttctcgtctg
                                                                        120
gcttttttct tcttttttat ttgtttggga gattcccagc tagtttcaga cttggtctgt
                                                                        180
gaaggaggca cactattttg cttggtattt gacttggatt tatctgtctc ttgtagtatt
                                                                        240
ggcggcactt gggaagagct cttgtcagaa tcactttttg ataagattac agatggctcg
                                                                        300
gtagaagtag cag
                                                                        313
      <210> 272
      <211> 462
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) . . . (462)
      \langle 223 \rangle n = A,T,C or G
      <400> 272
aaaaaacatt tattttaata agactattgc naacacatta aaaaaactaa atagtaatat
                                                                         60
tacaaaatct atatacttgc acatttagta tttgtcaatg tgccagaggt tttcttcatg
                                                                        120
aaatttgact tetttgaagt gaaggetttt ttetateate tettataget etgaetgaat
                                                                        180
aagtettaat getttettea tgttttetat caataggggt aaatecegag geteatatgt
                                                                        240
gtacaatctg ttagagtatc ttccagctat gtcagctcta actgttaaag aagggtctac
                                                                        300
aaacatgatt ctaggcacat attgcccatc aggtgataaa ttcttatcag tggtttcatg
                                                                        360
cataaggttt agcatgatga acttattctg agccatttct tgtatttctt cattttgggc
                                                                        420
aaatactttc tttagtgctt gagagtattg acaatcctcc ag
                                                                        462
      <210> 273
      <211> 282
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (282)
      <223> n = A, T, C or G
      <400> 273
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                                                                         60
tacatnneat tteatattat ataattetge ttattettte aaaaatttat acateeattg
                                                                        120
ggcaaggaat ggttttcatt aaattaccaa tattaaatgc acttaatcat tgtgtatagg
                                                                        180
ttaaaccaaa gtaactatta actaactttt aggcatttta aggaggtaaa acatacattt
                                                                        240
tacacataag tatttgatgc aaatatgcag ataaaatttt tt
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<210> 274
      <211> 125
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (125)
      <223> n = A, T, C or G
      <400> 274
cagocctaga cotcaactac ctaaccaacn tincttaaaa taaaatcccc actatgcaca
                                                                        60
ttnaatcnct ccaacatact cggattctac cctagcatca cacaccgcac aatcccctat
                                                                       120
                                                                       125
ctagg
      <210> 275
      <211> 528
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(528)
      <223> n = A, T, C or G
      <400> 275
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ataagccngg aaccacaaat aattaaaagg aaacacagca atcccataaa caagcattct
                                                                       120
ggcatctgtt agaaattttc cctcaaatta tgaaatgtag ctctccatgc tttccaatga
                                                                       180
ttgttataat acccacaaat atctgtgatt tcagtggaat actttaacaa aagttttctt
                                                                       240
tttaaqqcat qatcctqatt cattttttct tcaatatctc agtcatttca ggaactacct
                                                                       300
taaataaatc tgcaactatt ccataatctg ccacttggaa aattggagct tctgggtctt
                                                                       360
tattaattqc cacaattqtc ttqctqtctt tcatcccaqc taaatqttgg atggctccaq
                                                                       420
atattccaac agcaatataa agttctggtg ctactatttt tcccgtctgn ccaacttgca
                                                                       480
tgtcattggg aacaaagcca gcatcaacag cagcacggga agcaccaa
                                                                       528
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      <211> 420
      <212> DNA
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      <220>
      <221> misc feature
      <222> (1)...(420)
      <223> n = A,T,C or G
      <400> 276
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                                                                        60
agaaacctga taaaatatac ttttgtgaac aaaaattgag acatttacat tttctcccta
                                                                       120
tgtggtcgct ccagacttgg gaaactattc atgaatattt atattgtatg gtaatatagt
                                                                       180
tattqcacaa qttcaataaa aatctqctct ttqtatqaca qaatacattt gaaaacattq
                                                                       240
gttatattac caagactttg actagaatgt cgtatttgag gatataaacc cataggtaat
                                                                       300
aaacccacag gtactacaaa caaagtctga agtcagcctt ggtttggctt cctagtgtca
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attaaacttc taaaagttta atctgagatt ccttataaaa acttccagca aagcaacttt
                                                                       420
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<210> 277
      <211> 668
      <212> DNA
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      <223> n = A, T, C or G
      <400> 277
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atngcaccag accortgaatt crictagete etecaatece artitatece atggaaccae
                                                                       120
taaaaacaag gtctgctctg ctcctgaagc cctatatgct ggagatggac aactcaatga
                                                                       180
aaatttaaag ggaaaaccct caggcctgag gtgtgtgcca ctcagagact tcacctaact
                                                                       240
agagacagge aaactgcaaa ccatggtgag aaattgacga cttcacacta tggacagctt
                                                                       300
ttcccaagat gtcaaaacaa gactcctcat catgataagg ctcttacccc cttttaattt
                                                                       360
gtccttgctt atgcctgcct ctttcgcttg gcaggatgat gctgtcatta gtatttcaca
                                                                       420
agaagtagct tcagagggta acttaacaga gtatcagatc tatcttgtca atcccaacgt
                                                                       480
tttacataaa ataagagatc ctttagtgca cccagtgact gacattagca gcatctttaa
                                                                       540
cacagoogtg tgttcaaatg tacagnggtc cttttcagag ttggacttct agactcacct
                                                                       600
gttctcactc cctgttttaa ttcaacccag ccatgcaatg ccaaataata gaaattgctc
                                                                       660
cctaccag
                                                                       668
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      <211> 202
      <212> DNA
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      <220>
      <221> misc_feature
      <222> (1)...(202)
      <223> n = A, T, C or G
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                                                                        60
ttngcnaagt ggggtcccat caaggttcag tggcagtgga tctgggacag atttcactct
                                                                       120
cacgatcagc agtctgcaac ccgaagattt tgcaacttac tactgtcaac agagttacat
                                                                       180
gtccccgtac acttttggac cc
                                                                       202
     <210> 279
      <211> 694
      <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(694)
     <223> n = A,T,C or G
      <400> 279
ctgtacttgg acaaaataag ttaattctat ttggttgtcc attaaagttt tatgtggcta
                                                                       60
tgnacccact ggagctaaaa attggctttt aactgtttcc aaatcagaac tagcagagga
                                                                      120
gagaagtaaa taaagccaat ggcactccct tcagaggctc aaaatggtta gattttgatg
                                                                      180
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cagatttaac cttagcgagt ttcagtcagt ccatttagat gatcctgtag gtt atacactgaa ccgttggttt aacttctctt ccttcctcaa agtttatgat aactccctgtat tgggagtgac tgacataagt tcagatctgc tcagagtggc tgacacttaaggt cagtcagaaa ataatcaaac agacttctca tgtaagcacc gtgactaagacac tggctgctaa tcctggaata ccgctgtctg aattaacttt aggttttttccta aaggaaatat ctctgccaaa gaagtttcca gacagntgct tgggggaaaa ctggtcttt tgatccggtt ctttcangan taggtngaca aaaaaaagnct atccacgcn tttntcacct gggcccagcg gnnctcctcc nggaaacacangg gactcttccc ngggctngct tnng	agagactc 300 gtaaggaa 360 gactcaca 420 agctgtga 480 ggagatcc 540 agaaatnc 600
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<210> 281 <211> 398 <212> DNA <213> Homo sapien	
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aaatttgtta ggtctgaaga atctaaaact gttaatttaa cccttaactt gtgactacagcac atataaaata tgtaaacacc agcctgttgc tgtacttttc tgcacagcctcaa atatttctca ttatcttgtc acttagttct tcatgttct cctttaataatg gtaataggaa aacaaaaccc aaagcttttc agaacttcag tgtcctattttga caagttaact tgtaaatact caggttttac gatgtataat ttagaccaaacta actcatggag atattttgaa ctattatta ggtacaaact ttatgttagtatg tcataaaaata taacattaca gcttattt	ttatttt 120 ttctgact 180 tgaggttt 240 acctaata 300
<210> 282 <211> 226 <212> DNA <213> Homo sapien	
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aaaacaatat totottttig aaaatagtat naacaggoca tgoatataat gta ttacnocaat atgtaaagat tottoaaggt aacaagggtt tgggttttga aat tggatottat agacogttoa tacaatggtt ttagcaagtt catagtaaga caa ctatottttt ttttggotgg ggtgggggg cocaggooga ggotgg	aaacatc 120

<210> 283 <211> 358 <212> DNA

<213> Homo sapien

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aaacaaaaat actcaagatc atttatattt ttttggagag aaaactgtcc taatttagaa
                                                                       60
tttccctcaa atctgaggga cttttaagaa atgctaacag atttttctgg aggaaattta
                                                                      120
gacaaaacaa tgtcatttag tagaatattt cagtatttaa gtggaatttc agtatactgt
                                                                      180
actatecttt ataagteatt aaaataatgt tteateaaat ggttaaatgg accaetggtt
                                                                      240
tcttagagaa atgtttttag gcttaattca ttcaattgtc aagtacactt agtcttaata
                                                                      300
cactcaggtt tgaacagatt attctgaata ttaaaattta atccattctt aatatttt
                                                                      358
      <210> 284
      <211> 288
      <212> DNA
      <213> Homo sapien
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aaaacttttg ttaagaaaaa ctgccagttt gtgcttttga aatgtctgtt ttgacatcat
                                                                       60
agtotagtaa aattttgaca gtgcatatgt actgttacta aaagctttat atgaaattat
                                                                       120
taatgtgaag tttttcattt ataattcaag gaaggatttc ctgaaaacat ttcaagggat
                                                                       180
ttatgtetac atatttgtgt gtgtgtgtgt gtatatatat gtaatatgca tacacagatg
                                                                       240
                                                                       288
catatqtqta tatataatga aatttatgtt gctggtattt tgcatttt
      <210> 285
      <211> 629
      <212> DNA
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      <221> misc feature
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      <223> n = A, T, C or G
      <400> 285
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                                                                        60
                                                                       120
ccaaacatat aactgaactc ctcacaccca attggaccaa tctatcaccc tatanaagaa
                                                                       180
ctaatqttag tataagtaac atgaaaacat tctcctctgc ataagcctgc gtcagattaa
                                                                       240
aacactgaac tgacaattaa cagcccaata tctacaatca accaacaagt cattattacc
ctcactqtca acccaacaca qqcatqctca taaggaaagg ttaaaaaaag taaaaggaac
                                                                       300
teggeaaate ttaceeegee tgtttaceaa aaacateace tetageatea eeagtattaq
                                                                       360
aggcaccgcc tgcccagtga cacatgttta acggccgcgg taccctaacc gtgcaaaggt
                                                                       420
aqcataatca cttqntcctt aattagggac ctgtatgaat ggcttcacga gggttcagct
                                                                       480
qtctcttact tttaaccagt gaaattgacc tgcccgtgaa gaggcnggca tgacacagca
                                                                       540
agacgagaag accctatgga gctttaattt attaatgcaa acagnaccta acaaacccca
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caggicciaa actiacccaa accciggca
                                                                       629
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       <211> 485
       <212> DNA
      <213> Homo sapien
      <400> 286
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cgcaatttta ccttctgtct tttcagctac ccaggtgttt atgtgttttc tggacttctc 180 tacggcgctg ataaagtcaa gctcctccat ctctgcttgg tagaattttt ggcaggaatc 240 tctaaaagat gagaggaaat cacaagactt ttccccaaag agcctgttgg 290 <210> 289	ttaaaaccta tagcaatcat ttcaaatcta ttctgcaaat tgtataagaa taaagttaga attaacaatt ttattttgta caacagtgga attttctgtc atggataatg tgcttgagtc cctataatct atagacatgt gatagcaaaa gaaacaaaca aaagccagga aaacactcat tttcgccttg aatatgtaaa tgggattaat ttttgtcctgt gccttatgtg gaaaggaact tctttggttt tcctttttg ttctggtgga agcatgtgca ggagacatat catccaaaca taaaccatta aaatgtttgt ggtttgcttg gctgtaattt tcaaagtagt taattgagga caaagggtaa tgcagaagtg atagctttgg tttgctgagt cttgtttaa gtggccttga tattt	120 180 240 300 360 420 480 485
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<211> 384 <212> DNA	<210> 290	
<213> Homo sapien		
	<213> Homo sapien	
<220>	<220>	
<221> misc_feature	<221> misc_feature	

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<222> (1) ... (384)
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gtccctggat ctcctcaatg gtgtgcacaa tgaaggtgtc ctgcaggtcc tccatggccc
                                                                       120
cctccatcca gttgttgaag ggtgcagccc gcttggcata ctccaagtac aqctqqtcaa
                                                                       180
tggtctccag cagtttctcg gtccgctcca gagcttccct tcgcttctga gttaqqqccc
                                                                       240
ccagattgtc ccactggtca cagatctttt ggcaacgggc gttgacactg ggtgagtcat
                                                                       300
aatantocag otcattgago tootgtgoga tggoggoaat otgotocaca oggtootggt
                                                                       360
gggcagccag gccactctcg aagg
                                                                       384
      <210> 291
      <211> 278
      <212> DNA
      <213> Homo sapien
      <400> 291
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                                                                        60
gtaaatacta tatgttgaac aaattaaatg tcaaaatttt.ttattaccat agtccatgtt
                                                                       120
aatagtgggg ctttcaggtg tttagagatt ttttttgttg ttgttaacat tcattqcaaa
                                                                       180
agtactagat ggtgtataac tctagagttg aattttaagg gattccctaa tatgtatact
                                                                       240
atctttttat ctgaagtaat aaataaacaa tgatcttg
                                                                       278
      <210> 292
      <211> 177
      <212> DNA
      <213> Homo sapien
      <400> 292
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cctccgtttc ctgcttaagt gcattccgtg caatcgtctg.gaacgcctgc tccacgttga
                                                                       120
tggcctcctt ggcactggtc tcaaagtagg gaatgttgtt tttgctgtag caccagg
                                                                       177
      <210> 293
      <211> 403
      <212> DNA
      <213> Homo sapien
      <400> 293
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                                                                        60
tcaagtacca aaacgttgaa ttgatgatgc agttttcata tatcgagatg ttcgctcgtg
                                                                       120
cagtactgtt ggttaaatga caatttatgt ggattttgca tgtaatacac agtgagacac
                                                                       180
agtaatttta totaaattao agtgoagttt agttaatota ttaataotga otoagtgtot
                                                                       240
gcctttaaat ataaatgata tgttgaaaac ttaaggaagc aaatgctaca tatatgcaat
                                                                       300
ataaaatagt aatgtgatgc tgatgctgtt aaccaaaggg cagaataaat aagcaaaatg
                                                                       360
ccaaaagggg tcttaattga aatgaaaatt taattttgtt ttt
                                                                       403
      <210> 294
      <211> 305
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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<222> (1)...(305)
     <223> n = A, T, C \text{ or } G
     <400> 294
60
tatgggtgga agttggagag aaggacattt tggctttgta catgaaaaga ctctccagat
                                                                 120
agaaacagat tctgcccata agtgaaataa aatgctttgt gggggtaatg agtgacttat
                                                                 180
agtattcagg cagatgttac ataactgcta attaagtttc cctggattga ntttanncaa
                                                                 240
anaattgaaa gtngattttg gtcangtgtc agnaaactac tgcctataaa cccatatcnt
                                                                 300
accca
                                                                 305
     <210> 295
     <211> 397
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(397)
     <223> n = A, T, C or G
     <400> 295
cctatctggt tggccttttt gaagacacca acctgtgtgc tatccatgcc aaacgtgtaa
                                                                 60
caattatgcc aaaagacatc cagctagcac gccgcatacg tggagaacgt gcttaagaat
                                                                 120
180
cctgttattg gtagttctga acgttagata tttttttcc atggggtcaa aaggtaccta
                                                                 240
agtatatgat tgccgagtgg aaaaataggg gacagaaatc aggtattggc agtttttcca
                                                                 300
tttncatttg tgggngaatt tttaatataa atgcggagac gtaaagcatt aatgcnagtt
                                                                 360
aaaatgtttc agtgaacaag tttcagcggt tcaactt
                                                                 397
     <210> 296
     <211> 447
     <212> DNA
     <213> Homo sapien
     <400> 296
ccatcctcga tgttgaagtt gtcgtggggc ccgaagacgt tggtggggat gacagcggtg
                                                                 60
aaggtgcage cgtactgctg gaagtaggce ctgttctgca cgtcgatcat cctcttggca
                                                                 120
tacgagtacc caaaattgct gttgtgggga ggcccattgt ggatcatggt ctcatctatc
                                                                 180
gggtaggtcg tcttgtcagg gaagatacag gtggacaggc aggacaccac cttgcgggcg
                                                                 240
cccacctcga aggccgagtg caggacgttg tcgttcatgt gcacgttttt cctccagaag
                                                                 300
tccaaattgt atttgatatt ccggaacagg cccccacca ttgcagcaag atggatgacg
                                                                360
tgtgtgagtt ggaccttctc aaacagggcg cgggtctgtg ctgtatccgt gagatcggcg
                                                                420
tctttagagg agacaaacac ccagtcc
                                                                 447
     <210> 297
     <211> 681
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(681)
     <223> n = A,T,C or G
```

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<400> 297
aaataacagc atgtaaaata ttaaaataca agctttcaaa aataaataca taaataaqta
                                                                      60
gaaccctcgt aagaaatagt caaacacatt aagtcctttc cagctgtccc tagaaagctg
                                                                     120
ctgttctctt tttcattttc aqctctggta aggqcaqqqa ccaccctqca qqaaqtqtca
                                                                     180
atgatacgct gataagcttc ttacttctct cctgtcagtt ggtgctcccc ctgtgatgag
                                                                     240
aaaagggtta ctgttgcagg tgctaaggaa ggctgctctt ctgtcactct gaagttgctt
                                                                     300
ggagggatgt ccccatgcag actetetece agecetecae teagggaagg tetqtetqta
                                                                     360
cccactgcct tctatagcag aaaacttgca ctcctgaatg cttttttttt ttttcaaqaa
                                                                     420
agaagnggct gnggactcaa ctagattctt ggtttgaaaa agccaaaaca tattggtcac
                                                                     480
tgattgtcac attgggttag aaatgtccat tcatgatctc ccttaagctg cacacaaccc
                                                                     540
tatgaaataa ctaccattat ctaccctatt ttgctaaagc tcaaagagat taaataatgt
                                                                     600
tgacagggat citagcettg aactcactga aggngttact gcaaagttct gctcttcacc
                                                                     660
aagaaggntt acaggccaaa g
                                                                     681
     <210> 298
     <211> 353
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(353)
     <223> n = A, T, C \text{ or } G
     <400> 298
60
geoceaenet gneeceteee tgeocecaeg tetecageaa cacaaggegg ceagtggace
                                                                     120
gtgaaccatt tatttccaaa ctataaagaa acctgctctc tgagaaaana cactgcccaq
                                                                     180
gngatgaagc tccagcccct ggaggtccaa aacccagtcc aaactcagtc cctttagaaa
                                                                    240
gctgctgtgc cttggaaatg annntcggnt gtcanagcct gggaagtggt gggaagaacc
                                                                     300
ageceactee ceteteetge tgegatteea gegenegttg ggneeagate tgg
                                                                    353
     <210> 299
     <211> 560
     <212> DNA
     <213> Homo sapien
     <400> 299
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                                                                     60
acccagacac tgggctaggc tgcaacttta tctcatttaa tactcccagc tgtcatgtga
                                                                     120
gaaagaaagc aggctaggca tgtgaaatca ctttcatgga ttattaatgg atttaagagg
                                                                    180
gcatcaatca gctcaactca agatttcata atcattttta gtatttagat tgtgcctcaa
                                                                    240
agttgtagta ceteacaata cetecactgg ttteetgttg taaaaacett cagtgagttt
                                                                    300
gaccattgtg ctcttggctc ttgggctgga gtaccgtggt gagggagtaa acactaqaaq
                                                                    360
tetttagtac aaaactgete tagggacace tggtgattee tacacaagtg atgtttatat
                                                                    420
ttctcataaa gagtcttccc tatcccaagg tcttcatgat gccagtagcc atatatgata
                                                                    480
aattatgttc agtgataact tagttatcag aaatcagctc agtggtcttc cccgccatga
                                                                    540
ttcacatttg atgagttttt
                                                                     560
     <210> 300
     <211> 165
     <212> DNA
     <213> Homo sapien
     <220>
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<221> misc_feature
      <222> (1)...(165)
      <223> n = A,T,C or G
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attctaatat attactaagg caattttaat gaattaccat gtatataaaa aaatatctgn
                                                                       120
cacttggcac acaggtttgt atgtatgtgt atatatatat gtatg
                                                                       165
      <210> 301
      <211> 438
      <212> DNA
      <213> Homo sapien
      <400> 301
aaaatatatg tatttaaaaa caaaaagcaa cagtaatcta tgtgtttctg taacaaattg
                                                                       60
ggatctgtct tggcattaaa ccacatcatg gaccaaatgt gccatactaa tgatgagcat
                                                                       120
ttagcacaat ttgagactga aatttagtac actatgttct aggtcagtct aacagtttgc
                                                                       180
ctgctgtatt tatagtaacc attttccttt ggactgttca agcaaaaaag gtaactaact
                                                                       24C
gcttcatctc cttttgcgct tatttggaaa ttttagttat agtgtttaac tgqcatqqat
                                                                       300
taatagagtt ggagttttat ttttaagaaa aattcacaag ctaacttcca ctaatccatt
                                                                       360
atcetttatt ttattgaaat gtataattaa ettaaetgaa gaaaaggtte ttettgggag
                                                                       420
tatgttgtca taacattt
                                                                       438
      <210> 302
      <211> 172
      <212> DNA
      <213> Homo sapien
      <400> 302
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                                                                       60
accacaagtc caattgctat ggttacttca ggaagctgag gaactggtct gatgccgagc
                                                                       120
togagtgtca gtottacgga aacggagccc acctggcatc tatcctgagt tt
                                                                       172
      <210> 303
      <211> 552
      <212> DNA
      <213> Homo sapien
      <400> 303
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ggatcttttc atcctaccag atgagaaagg gaatgagtga atggagtgac cccgcaccct
                                                                       120 .
gtcactttcc tgagacatga ctgccaggaa gaagagctgc tctggtctcc atcagggctg
                                                                       180
gcaggacaaa ctgaccagtg agtcagtagg cagagttcac actgaaaaag ggcacaaggg
                                                                       240
ctgtcccaca atgggaggaa atggggtctc agaacttcta cttctctgaa aactaagaca
                                                                       300
caattgggac aaccaccacc cccgtgtgag atttctcacc tcgagacagg acaagatgaa
                                                                       360
gttcacggct tcttctgggg taaagacctt gaagagccca tcacaggcca acaaaatgaa
                                                                      420
cctacaacac cagggagaaa tataaacggg ttttaggccc aaccaaaaaa taaaaaataa
                                                                       480
aaaaagggcc tggagatgga gataaaataa atatttgtcc aactattcaa aggctaaggt
                                                                      540
ttttttttct tt
                                                                       552
      <210> 304
      <211> 601
```

<212> DNA

<213> Homo sapien

```
<400> 304
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tgggaagaaa ttcccacatg agattcataa attcttagac tccgtggctt ctttggtccg
                                                                       120
gaatgcttaa actcatatga gtgttctgga tcccagtgta tccaatcata attcacatta
                                                                       180
tcaccttcac gaaccacata ctttgcccac ggtgaaatac gatacaagat ctctccgctt
                                                                       240
ttactagtaa taactacctt taatttggat ccatgaggca cgagtacaga tttattctgc
                                                                       300
tttggtggga tatacagctc ccattttcca taatccagtt ttttgtatgg gtacgaaaat
                                                                       360
ggattccaac cattaaaatc tccagtaaga aaaactcctt ctgctcccgg ggcccattct
                                                                       420
ttgcagtata aaccaccatc agcacatctg tggacgccaa atgattcata gcctctggaa
                                                                       480
aacttatcaa taccaccttc attttctcca atgttcttca aaatttggct aaactgctta
                                                                       540
tacctgcgct ggaagtccac ggcgtagggc ttcaagtacc ggtcgatctc caggagtctg
                                                                       600
                                                                       601
      <210> 305
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 305
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                                                                       60
gaaccctcgt aagaaatagt caaacacatt aagtcctttc cagctgtccc tagaaagctg
                                                                      120
ctgttctctt tttcattttc agctctggta agggcaggga ccaccctgca ggaagtgtca
                                                                      180
atgatacgct gataagcttc ttacttctct cctgtcagtt ggtgctcccc ctgtgatgag
                                                                      240
aaaagggtta ctgttgcagg tgctaaggaa ggctgctctt ctgtcactct gaagttgctt
                                                                      300
ggagggatgt ccccatgcag actototocc agccctccac tcagggaagg totgtotgta
                                                                      360
cccactgcct tctatagcag aaaacttgca ctcctgaatg c
                                                                      401
      <210> 306
      <211> 313
      <212> DNA
      <213> Homo sapien.
      <400> 306
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taattcatga ggatctttca	tattaaaatt	taaccttaag	attcaaccgc	catgtgcttt	240
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ttcctagcca tgcactactn accagacncc tcaacngcct tttnatcaat nggncacatn	180
actoganach taaathatgg otgaatoato ogctacotho acgocaatgg cagootcaat	240
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according objective obtained 333+3-33	
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tgactctgga gctgcacagc gagggcacca ccgtcctgct cttccagttc gggatgaatg	180
caagttctag ccggtttttc ctacaaggaa ttcagttgaa tacaattctt cctgacgcca	240
gagaccetge etttaaaget gecaaegget eeetgegage getgeaggee acagteggea	300
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attgctctcc aagagaagga tgtggatggc ctggaccgca cagctggtgc aattcgaggc	180
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gcagtgctga tgataaggac ccctgaggag ttggatgact ctgactttga gacagaagat	480
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ccaattatag ctatcaggga tatacaaatt aaaaccaaaa tgaaacatca ctacacaccg	180
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aactetetat aatatteaa taatetaaet ggteteaatg eetgtagtag aaattgeaga	600
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                                                                      120
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cgttagecce tetecteecg gatggteatg tttttgteac attagagaat aaacagecac
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agcatatgaa tc
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gtcagtgggc tgctctggcc ctggtgtgca cggctgtggc agctgttgat gccagtqtcc
                                                                      240
tctaactcat gctgtccttg tgattaaaca cctctatctc ccttgggaat aagcacatac
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aggettaage tetaagatag ataggtgttt gteettttae categageta etteecataa
                                                                      360
taaccacttt gcatccaaca ctcttcaccc acctcccata cgcaagggga tqtqqatact
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tggcccaaag taactggtgg taggaatctt agaaacaaga ccacttatac tgtctgtctg
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canctatttg ntcctcctcc cccaccccag nccccaactt catgcttntc ttccgcnctc
                                                                       180
agecneectg coetgteete geggtgagte antgaceaen gntteecetg cangageege
                                                                       240
cgggcgtgag acncngacce tenntgcata caccaggccg ggcccnngct ggctcccccn
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gnggccctgt gaaanagctg g
                                                                       321
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      <211> 255
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atgtgcccgg cttggcagct gtgtagaaga tgtcataggt tccatcttca ttctcaatga
                                                                       120
categgeete ggeeteagtg ceatetgggg teagaacegt geaggteact ttaceettee
                                                                       180
cggcagtett ggcateaace acaaageeta ettettegee agtttteaca gtggaggega
                                                                       240
ttccaggacc cgtag
                                                                       255
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                                                                       60
tgaatttatt aatacagcat taagtttctt tgtgtnaaaa aatctttgtn cncagtaata
                                                                      120
aaaaaagata aggcaagatg cattaaacat gaaaccttct ggctcttttc ctctgcgttt
                                                                      180
ttacagagcc actgatgact atctgcaaca aaagagttaa gtttctgatt ttccgtatca
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ggtgatggnc tttggcactt atgctggcaa actgagcttc tttcccttga gtacttttgn
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aatgtacaag tagaagaagt cacaagtata ggatggtctg gactacgccg gccaccacag
                                                                      420
caatgaggtc aaagaagccc tcaaagnaga agcgnccaga tccagttgac aagatacaaa
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gcacgataga ggccca
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tetgtgacca gtgggacaat etgggggeee taaeteagaa gegaagggaa getetggage
                                                                      180
ggaccgagaa actgctggag accattgacc agctgtactt ggagtatgcc aagcgggctg
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caccetteaa caactggatg gagggggcca tggaggacet gcaggacace ttcattgtgc
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ttgnacttgg ncacttttgt gcttgaggag gcccattttc tgcctggcag ggggcaggta
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tgtgccctcc cgctgactcc tgctgtgtcc tgaggtgcat ttcctgttgn ncacacaang
                                                                      240
gecangnice attetecete cettiteace agngecaean ceinnicigg aaaaangaee
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acattgggga cacattgagc agggctgaaa gaatcaggat teetgaacet tggatcacae
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ctccagattt gcaagagaaa atccacattt ttgcccaaaa atgtctattt ttgacggaga.
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PCT/US99/30909 109

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agtaatttta totaaattao agtgoagttt agttaatota ttaataotga otoa	gtgtct 240
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congeniate tanagerage and agency galaalage generate cross	gccttc 18.0
gatggtccgc acggttgagg attctacgtg gttctcttgg ttcccctggt gtgt	aaggtt 240 gtgtgt 300
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gatcaaattt cctctgcttc ttttccaggt tggacacgag ttgccgctgg ttgtc	:caaat
180caacaaccag gtcgtccagc tcctgctgaa gcctgttctt ggtcttttcc agt 240	ttatcat
aageggeege etteteeteg tactgetggg tgaggntete gateteette tggaa	acctct 300
tettececte ttecagaget tecaeggnge tggcaaagte etgeagette ttett	cgagt 360
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ctttcaacag cagccctagt aatggtggag ttgttaatta atgtgtatat tgtac	tgaat 180
ttctgtcagt taaggggttc actgctttgg tggaaattgg tggaaattgc tagca	iggttc 240
cacgatgttt attttttttt ccatgttgta tatcattacc atttcacata cgcgt	ttcta 300
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                                                                       120
tggggtcccc aggatgaaaa cgacaatgtg cctttttatt attatttatt tggtggtcct
                                                                       180
gtgttattta agagatcaaa tgtataacca cctagctctt ttcacctgac ttagtaataa
                                                                       240
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                                                                       300
tgcctgtccc ccaggtggtg ggaataattt acaatctgtc caaccagaaa agaatgtgtg
                                                                       360
tgtttgagca gcattgacac atatctactt tgataagaga cttcctgatt ctctaggtcg
                                                                       420
gttcgtggtt atcccattgt ggaaattcat cttgaatccc attgtcctat agtcctagca
                                                                       480
ataagagaaa tttcctcaag tttccatgtg cggttctcct agctgcagca atactttgac
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gccattatat tigattitige attactigtti cacaatgaag etticittaa ggettigatt
                                                                      180
tttatgatta tgaaagaaat aaggcacaac cacagttttt ctttcttaaa tttcatcact
                                                                      240
gttgatgtgg ttcttttgtg ttaaaaaaaa aaagtgcaac tatcaaaact aaaaaattat
                                                                      300.
agagtaatat tgccgttctg ctgatttt
                                                                      328
      <210> 364
      <211> 569
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      <213> Homo sapien
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                                                                      120
ggaacagact cccttttcta aaactgaact tgaccacatc aaaagtttgt aaaacaatct
                                                                      180
ccatggtaat taaacttgca ttcaacacca tatggtaaca gaagatggca aaggataaga
                                                                      240
ttcagatctt agatctttcc aagtagggca tgttagatga tagaaggatt agttgcaagc
                                                                      300
tggatctgag ctcaggcttg ggcatgaagg aaactgtctc ccatgtggtt tggaagagtt
                                                                      360
aggggctccc tgagctctat tgtgaactat acgggtttca tccaaggaat ggtatgatgt
                                                                      420
gggcataaaa ccattcttca gacaactgaa gatggtcccc ttctgtagcc agaaacacta
                                                                      480
gctgtcctgc attgtccatt tcctttagcc ccaggcggtc ctgtgtgtac agggaggtct
                                                                      540
cctgtaaggg aatggtttcc ttggcttgg
                                                                      569
      <210> 365
      <211> 151
      <212> DNA
      <213> Homo sapien
      <400> 365
aaaaaaaaaa atccttttat tatggaattt gtcaaacaca cacacaagca taacaaaccc
                                                                       60
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ctaggtaccc atctccaagt tttgacccct attataattt catcttcagt gttttattat
                                                                       120
ccacttcctc tctctctatc tttagtattt t
                                                                       151
      <210> 366
      <211> 508
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (508)
      <223> n = A,T,C or G
      <400> 366
agtataaaga tatattccat aaaagagttt ggcagtcaaa ganaagcatc gcacttccga
                                                                        60
aaaacacaag cattcttctc ctagtctaca gagaattgng taaaaaaaaa aaaaaatcat
                                                                       120
catcaacagc cnccantnta cnccacacta gaargtacac tccggcaagt aaattaaggn
                                                                       180
tgcagtccat ccctgaacga tganaagngg tctgagctat ggcaaagngt tanaaagtag
                                                                       240
cccagctana caaatgcccc agctatcccc aggggagtta ttcagtactt aanacttcat
                                                                       300
ttccaananc agccccggaa aagccctgac aggaaggggg gaccagngat caccgatntc
                                                                       360
ccattagggg cggncaccaa aaacaaaatg cctggagctt ntgagcagct gcagcctggg
                                                                       420
gttgtggcta ggcncngggn gnggttgcaa aaaaacggct gtntccgggg agaggcaaat
                                                                       480
ggcaggccag ccagccctgg gtacatgg
                                                                       508
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      <211> 382
      <212> DNA
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                                                                       120
attgaccact gggatgcagt caacctggaa tgctttgaag aggacccagg gcgcaagtgg
                                                                       180
atggacaget tgeteagtaa ettggggtge eagtetgeet eteatqtagg gecetteate
                                                                       240
gatagetace getgetteea accaaageag gagggggeet teacetgetg gteageagte
                                                                       300
actggcgccc gccatctcaa ctatggctcc cggcttgact atgtgctggg ggacaggacc
                                                                       360
ctggtcatag acacctttca gg
                                                                       382
      <210> 368
      <211> 174
      <212> DNA
      <213> Homo sapien
      <400> 368
ccttctccct ctttgacaag gatggagatg gcactatcac caccaaggag ttggggacag
                                                                        60
tgatgagate cetgggacag aacceeactg aagcagaget geaggatatg ateaatgagg
                                                                      120
tggatgcaga tgggaacggg accattgact tcccggagtt cctgaccatg atgg
                                                                      174
      <210> 369
      <211> 216
      <212> DNA
      <213> Homo sapien
      <400> 369
aaatctcatg ggttctatta aaaaaatata tatatagggc cccaatccat tgccatcaaa
                                                                        60
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ttgcccttgg acttttccaa ggtatattat ggggttttat gcaaaattcc aagctaccat

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gtaacttttt ttaaccattt aacaaggagg gggaactgtt tcctaccttc tttacatgtt
                                                                      180
gtgcattgtt gtggtccaga aatgccaaac cttttt
                                                                      216
      <210> 370
      <211> 344
      <212> DNA
      <213> Homo sapien
      <400> 370
ccttggtcag gatgaagttg gctgacacag cttagcttgg ttttgcttat tcaaaagaga
                                                                       60
aaataactac acatggaaat gaaactagct gaagcctttt cttgttttag caactgaaaa
                                                                      120
ttgtacttgg tcacttttgt gcttgaggag gcccattttc tgcctggcag ggggcaggtc
                                                                      180
tgtgccctcc cgctgactcc tgctgtgtcc tgaggtgcat ttcctgttgt acacacaagg
                                                                      240
gccaggetee atteteeste cettteeace agtgccacag cetegtetgg aaaaaggace
                                                                      300
aggggtcccg gaggaaccca tttgtgctct gcttggacag cagg
                                                                      344
      <210> 371
      <211> 741
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(741)
      <223> n = A,T,C or G
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                                                                      60
gctaagtgta gcagtttgtt ccctgctaca ctccaaggca caaaggagtt caaggaatgt
                                                                      120
gcaatggaaa tcagttagat gaatgtgtta ggaaccttcc ctttaataaa gctggatccc
                                                                      180
acactagece etacacecte teateaceaa atatteetge treeteteae etgeaettge
                                                                      240
tgttctctcc tctgccacac aaatctacct ctcaagccta ggtcccacct gcttcatgac
                                                                      300
aactttccag actattccag aacctttaac catctctgac ctctcatcag atctatgttg
                                                                      360
tacataacac caattaatga gatcattact gctttatgct ctaattgctt cctgtattca
                                                                      420
aaatottoto tocaaccaca taatgactoo ctaaacttot ottotatttt ccaatgoott
                                                                      480
gtacaagcac agaactggtc aatcaataaa tactcactgg ttatttgagg aaaaaatgtt
                                                                      540
gccaagcacc atctttatca gaaaataaat caattcttct aaacttggag aaatcaccct
                                                                      600
attcctagta tgtgatctta attagaacaa ttcagattga gaangngaca gcatgctggc
                                                                      660
agtectcaga gecetegett geteteggna cetecetgee tgggetecca etttqqtqqe
                                                                      720
atttgaggag cccttcagcc t
                                                                      741
      <210> 372
      <211> 218
      <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(218)
     <223> n = A, T, C or G
     <400> 372
ecgccagtgt getggaatte gecettggee geeegggeag gtaceacaac ageaggnetg
                                                                       60
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agtgagaaat ctaccacctt ctacagtagc cccagatcac cggacacaac actctcacct 120 gccagcacga caagetcagg cgtcagtgaa gaatccacca cctcccacag ccgaccaggc 180 tcaacgcaca caacagcatt ccctggcagt accttggn 218 <210> 373 <211> 168 <212> DNA <213> Homo sapien <400> 373 actgctaggg aatgctgttg tgtgcattga gcctggtcgg ctgtgggagg tggtggattc 60 ttcactgacg cctgagcttg tcgtgctggc aggtgagagt gttgtgtccg gtgatctggg 120 gctactgtag aaggtggtag atttctcact caggcctgct gttgtggt 168 <210> 374 <211> 154 <212> DNA <213> Homo sapien <220> <221> misc_feature <222> (1)...(154) <223> n = A, T, C or G<400> 374 tgagasatet accacettet acagngagee ceanateace ggacacaaca eteteacetg 60 ccagcacgae aageteagge gteagtgaag aateeaceae eteccacage egaccagget 120 caacgcacac aacagcattc cctggcagta cctc 154 <210> 375 <211> 275 <212> DNA <213> Homo sapien <400> 375 actgccaggg gacagtgctg tgtcagttga acctgggctg ctgtgggaag ttgttgattc 60 ctgactgggg cctgaggtgg tggtgctggc aggtaacagt gttgtatccg ttgagcctgg 120 gctgctgtgg gaagttgtag aatgccgact gaggcctggc gtggtggtgc tgtcagggaa 180 tgctgttgtg tgcgttgagc ctggtcggct gtgggaggtg gtggattctt cactgacgcc 240 tgagcttgtc gtgctggcag gtgagagtgt tgtgg 275 <210> 376 <211> 191 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1)...(191) <223> n = A, T, C or G<400> 376 actgccaggg gacagtgctg tgtcagttga acctgagctg ctgtgggaag ttgttgattc 60 ctgactggag cctgaggtgg tggtgctggc aggtaacagt gttgtatccg ttgagcctgg 120 gctgctgtgg gaagttgtag aatgccgact gaggcctgcc gtggtggtgc tgntagggaa 180

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tgctgctagc g
                                                                     191
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      <212> DNA
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tgttaatttc ctgcagctcc tggttggttc tggagcagat gatctcaatg agagagtcct
                                                                     120
cgtcggttcc cagccccttc atggaagctt ttagctcaga agcgtcatac tgagcaggtg
                                                                     180
tettematag geceaaaate acegteteea ggtggecaga taaggetgae tteagtgetg
                                                                     240
atgcaagttc ctttttggtc cttctctggt aggcgaaggc aatatcctgt ctctgtgcat
                                                                     300
tgctgcggtt ggtcaaaatg ttgacaatgg tgacctcatc cacacctttg gtcttgatgg
                                                                     360
ctgtttcaat gttcaaagca tcccgctcag catcaaagtt agtataggct ttgacagacc
                                                                     420
catatgcact tgggggtgta gagtgatcac cctccaagcc gagcttgcac aggatt
                                                                     476
      <210> 378
      <211> 455
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(455)
      <223> n = A, T, C \text{ or } G
      <400> 378
agtgtgctgg aattcgccct tggccgcccg ggcaggtaca catcccatct tcaaatttaa
                                                                      60
aatcatattg tcagttgtcc aaagcagctt gaatttaaag tttgtgctat aaaattgtgc
                                                                     120
aaatatgtta aggattgaga cccaccaatg cactactgta atatttcgct tcctaaattt
                                                                     180
cttccaccta cagataatag acaacaagtc tgagaaacta aggctaacca aacttagata
                                                                     240
300
agaaacaaat ttcaaaaataa atcacatctt ctcttaaaac ttggcaaacc cttccctaac
                                                                     360
tgtccaagtn tgagcataca ctgccactgg ctttagatac tccaattaaa tgcactactc
                                                                     420
tttcactggt ctgaatgaag tatggtgaaa caagc
                                                                     455
      <210> 379
      <211> 297
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(297)
      \langle 223 \rangle n \approx A,T,C or G
      <400> 379
ageteggate cetagnaegg eegecagtgt getggaatte gecettageg geggeeeggg
                                                                      60
caggtacaaa gaatccttag acgccatact gagttttaag ttccttaatt cctaatttaa
                                                                     120
ggcttctagt gaagcctcct cacagtaggc ttcactaggc ccacagtgcc cctagacctc
                                                                     180
tgacaatccc accctagaca gactttattg caaaatgcgc ctgaagaggc agatgattcc
                                                                     240
caagagaact caccaaatca agacaaatgt cctagatctc tagtgtggna gaactat
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<210> 380

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<211> 144
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(144)
      <223> n = A,T,C or G
      <400> 380
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                                                                        60
ctattttttt gngttttttt gtttttaaat caataagtaa tctaggacta gcattatgtt
                                                                       120
tgctagacct ggcatttgct cggc
                                                                       144
      <210> 381
      <211> 424
      <212> DNA
      <213> Homo sapien
      <400> 381
actictigaat acaagittict gataccactg cactgictga gaatticcaa aactitaatg
                                                                        60
aactaactga cagcttcatg aaactgtcca ccaagatcaa gcagagaaaa taattaattt
                                                                       120
catgggacta aatgaactaa tgaggataat attttcataa ttttttattt gaaattttgc
                                                                       180
tgattettta aatgtettgt tteecagatt teaggaaaet ttttttettt taagetatee
                                                                       240
acagettaca geaatttgat aaaarataet titgtgaaca aaaattgaga catttacatt
                                                                       300
ttctccctat gtggtcgctc cagacttggg aaactattca tgaatattta tattgtatgg
                                                                       360
taatatagtt attgcacaag ttcaataaaa atctgctctt tgtataacag aatacatttg
                                                                       420
aaaa
                                                                       424
      <210> 382
      <211> 408
      <212> DNA
      <213> Homo sapien
      <400> 382
actittgaat acaagttict gataccactg cactgictga gaatticcaa aactitaatg
                                                                        60
aactaactga cagcttcatg aaactgtcca ccaagatcaa gcagagaaaa taattaattt
                                                                       120
catgggacta aatgaactaa tgaggataat attttcataa ttttttattt gaaattttgc
                                                                       180
tgattcttta aatgtcttgt ttcccagatt tcaggaaact ttttttcttt taagctatcc
                                                                       240
acagettaca geaatttgat aaaatataet tttgtgaaca aaaattgaga catttacatt
                                                                       300
ttctccctat gtggtcgctc cagacttggg aaactattca tgaatattta tattgtatgg
                                                                       360
taatatagtt attgcacaag ttcaataaaa atctgctctt tgtatgac
                                                                       408
      <210> 383
      <211> 455
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(455)
      <223> n = A, T, C or G
      <400> 383
actettgaat acaagtttet gataceactg cactgtetga gaatttecaa aactttaatg
                                                                        60
```

aactaactgn cnncttcatg aaactgtcca ccaagatcaa gcagagaaaa taattaattt catgggacta aatgaactaa tgaggataat attttcataa ttttttattt gaaattttgc tganncttta aatgtcttgt ttcccagatt tcaggaaact ttttttcttt taagctatcc acagcttata gcaatttgat aaaatatact tttgtgaaca aaaattgaga catttacatt ttctccctat gtggtcgctc cagacttggn aaactattca tgaatattta tattgtatgg taatatagtt attgcacaag ttcaataaaa atctgctctt tgtataacag aatacatttg aaaacattgg ttatattacc aagactttga ctaga	120 180 240 300 360 420 455
<210> 384 <211> 376 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(376) <223> n = A,T,C or G	
<400> 384 actcttgaat acaaggttct gatatcactg cactgtctga gaatttccaa aactttaatg aactaactga cagcttcatg aaactgtcca ccaagatcaa gcagagaaaa taattaattt catgggacta aatgaactaa tgaggataat attttcataa ttttttattt gaaattttgc tgattctta aatgtcttgt ttcccagatt tcaggaaact ttttttttt ttaagctatc cacagcttac agcaatttga taaaatatac ttttgngaac aaaaattgag acatttacat tttctcccta tgtgggcgct ccagacttgg gaaactattc atgaatattt atattgnatg ggaatatagc attgcc	60 120 180 240 300 360 376
<210> 385 <211> 422 <212> DNA <213> Homo sapien	
<pre><400> 385 acctgtgggt ttattaccta tgggtttata tcctcaaata cgacattcta gtcaaagtct tggtaatata accaatgttt tcaaatgtat tctgtcatac aaagagcaga tttttattga acttgtgcaa taactatatt accatacaat ataaatattc atgaatagtt tcccaagtct ggagcgacca catagggaga aaatgtaaat gtctcaattt ttgttcacaa aagtatattt tatcaaattg ctgtaagctg tggatagctt aaaagaaaaa aagtttcctg aaatctggga aacaagacat ttaaagaatc agcaaaattt caaataaaaa attatgaaaa tattatcctc attagttcat ttagtcccat gaaattaatt attttctctg cttgatcttg gtggacagtt tc</pre>	60 120 180 240 300 360 420
<210> 386 <211> 313 <212> DNA <213> Homo sapien	
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<210> 387
      <211> 236
      <212> DNA
      <213> Homo sapien
      <400> 387
egeceteata ateatettee tratergett ectagteetg targecettt tectaacaet
                                                                     60
cacaacaaaa ctaactaata ctaacatctc agacgctcag gaaatagaaa ccgtctgaac
                                                                     120
tatectgeec gecateatee tagtecteat egeceteeca tecetaegea teetttacat
                                                                    180
aacagacgag gtcaacgatc cctcccttac catcaaatca attggccacc aatggt
                                                                    236
      <210> 388
      <211> 195
      <212> DNA
      <213> Homo sapien
      <400> 388
acgccctttt cctaacactc acaacaaaac taactaatac taacatctca gacgctcagg
                                                                     60
aaatagaaac cgtctgaact atcctgcccg ccatcatcct agtcctcatc gccctcccat
                                                                    120
180
ttggccacca atggt
                                                                    195
      <210> 389
      <211> 183
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(183)
      \langle 223 \rangle n = A,T,C or G
      <400> 389
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                                                                     60
cetgaactat cetgecegee atcatectag tecteatege ecteceatee etaencatee
                                                                  120
tttacataac agacgaggtc aacgatccct cccttaccat caaatcaatt ggccaccaat
                                                                    180
ggt
                                                                    183
      <210> 390
      <211> 473
      <212> DNA
      <213> Homo sapien
     <400> 390
acaaagcagc aactgcaata ctcaaggtta aaacattaga aaagcatttg tgtgacaggt
                                                                     60
atattacagt attatcaaaa tattacattt tcagacttac ttagcagata atcatccacc
                                                                    120
agagettaaa tetttaaatt attteeatag tettaaaaaa tatgtaatgt cagaatgeat
                                                                    180
ataaaaagaa tgtaaaagga aacctaaaat acaaatggaa taatgtaaca aataaatatt
                                                                    240
tgatttcagt aactgttaat aatcagctca acaccaccat tctctctaaa ctcaatttaa
                                                                    300
ttcttatagg aataatgaac tgtcaaatgc catggcataa ttatttattt ccaagctatc
                                                                    360
atcaatgatt agaactaaaa aaaatttggc ataaaaaaat cacaattcag cataaataaa
                                                                    420
gctattttta gcttcaacac tagctagcat ctctaagaat tgttgaaata agt
                                                                    473
     <210> 391
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<210> 391 <211> 216 WO 00/37643 PCT/US99/30909 118

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<212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(216)
      <223> n = A, T, C or G
      <400> 391
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                                                                         60
ttaagactat ggaaataatt taaagattta agctctggtg gatgattatc tgctaagtaa
                                                                        120
gtctgaaaat gtaatatttt gataatactg taatatacct gtcacacaaa tgcttttcta
                                                                        180
atgttttaac cttgagtatt gcagttgctg ctttgt
                                                                        216
      <210> 392
      <211> 98
      <212> DNA
      <213> Homc sapien
      <400> 392
acttatttca acaattctta gagatgctag ctagtgttga agctaaaaat agctttattt
                                                                         60
atgctgaatt gtgatttttt tatgccaaat tttttaa
                                                                         98
      <210> 393
      <211> 397
      <212> DNA
      <213> Homo sapien
      <400> 393
tgccgatata ctctagatga agttttacat tgttgagcta ttgctgttct cttgggaact
                                                                        60
gaactcactt tcctcctgag gctttggatt tgacattgca tttgaccttt tatgtagtaa
                                                                       120
ttgacatgtg ccagggcaat gatgaatgag aatstacccc cagatccaag catcctgagc
                                                                       180
aactottgat tatocatatt gagtcaaatg gtaggcattt cotatcacct qtttccattc
                                                                       240
aacaagagca ctacattcat ttagctaaac ggattccaaa gagtagaatt gcattgaccg
                                                                       300
cgactaattt caaaatgctt tttattatta ttatttttta gacagtctca ctttgtcgcc
                                                                       360
caggccggag tgcagtggtg cgatctcaga tcagtqt
                                                                       397
      <210> 394
      <211> 373
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(373)
      \langle 223 \rangle n = A,T,C or G
      <400> 394
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                                                                        60
tggatttgac attgcatttg accttttatg tagtaattga catgtgccag ggcaatgatg
                                                                       120
aatgagaatc tacccccaga tccaagcatc ctgagcaact cttgattatc catattgagt
                                                                       180
caaatggtag gcatttccta tcacctgttt ccattcaaca agagcactac attcatttag
                                                                       240
ctaaacggat tccaaagagt agaattgcat tgaccacgac tantttcaaa atgcttttta
                                                                       300
ttattattat tttttagaca gtctcacttt gtcgcccagg ccggagtgca gtggtgcqat
                                                                       360
ctcagatcag tgt
                                                                       373
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<212> DNA

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<210> 395
      <211> 411
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(411)
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      <400> 395
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aactaacctc ctcggactcc tgcctcactc atttacacca accacccaat tatctataaa
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aactaacctc ctcggactcc tgcctcactc atttacacca accacccaac tatctataaa
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cctagccatg gccatcccct tatgagcggg cgcagtgatt ataggctttc gctctaagat
taaaaatgcc ctagcccact tcttaccaca aggcacacct acacccctta tccccatact
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ggcttttatc cttcatgggt tatgatgttc tcctgatgac acatttctct gagttttgta ... 420
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	tcccctatca	_		_		180
	acatgctcat				-	240
	ctgtaaagta					300
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gatggctttt tagatagttc tatactgctg tattgtgtta gcacttttct ttgtcattaa
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2 23 - 33 udeaccocca caccaccac acayaayaac	100

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                                                                      300
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cagatatttt tgtttctcat cttaactatc caagccacct attttatttg ttctttcatc
                                                                      240
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agactgtgtc agacatctct gcaattcatc agcatctatc tgcccatcct gtccagctac
                                                                      360
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g
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2117 278	

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240

278

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aatcactgtc ttgccccagg ctccggtgtg actcgtgcag ccatcgacag tgacgctgta 120
ggtgaagegg ctgttgccct cggcgcggat ctcgatctcg ttggagccct ggaggagcag 180
ggccttcttg aggttgccag tctgctggtc catgtaggcc acgctgttct tgcagtggta 240
ggtgatgttc tgggaggcct cggtggacat caggcgcagg aaggtcagct ggatggccac 300
ateggeaggg teggageeet ggeegeeata etegaaetgg aatecategg teatgetete 360
geogaaccog acatgeetet tgteettggg gttettgetg atgtaccagt tettetggge 420
cacactgggc tgagtggggt acacgcaggt ctcaccagtc tccatgttgc agaagacttt 480
gatggcatcc aggttgcagc cttggttggg gtcaatccag tactctccac tcttccagtc 540
agagtggcac atcttg
<210> 463
<211> 659
<212> DNA
<213> Homo sapiens
<400> 463
cacactgtgc ccttccagtt gctggcccgg tacaaaggcc tgaacctcac cgaggatacc 60:
tacaageeee ggatttacae etegeeeace tggagtgeet ttgtgacaga cagtteetgg 120
agtgcacgga agtcacaact ggtctatcag tccagacggg ggcctttggt caaatattct 180
tetgattact tecaageece etetgaetac agatactace ectaecagte ettecagaet 240
ccacaacacc ccagetteet ettecaggac aagagggtgt cetggteect ggtetacete 300
cccaccatcc agagetgetg gaactacgge ttetectget cctcggacga getecetqte 360
ctgggcctca ccaagtctgg cggctcagat cgcaccattg cctacgaaaa caaagccctg 420
atgetetgeg aagggetett egtggeagae gteacegatt tegagggetg gaaggetgeg 480
atteccagtg ccetggacac caacayeteg aagagcacet ceteetteec etgeceqqca 540
gggcacttca acggcttccg cacggtcatc cgccccttct acctgaccaa ctcctcaggt 600
gtggactaga cggcgtggcc caagggtggt gagaaccgga gaaccccagg acgccctca 659
<210> 464
<211> 695
<212> DNA
<213> Homo sapiens
<400> 464
accttcattt gaccccatca gcttcagggc cttctttaca tttccactgg cctgatccat 60
gtatgcaatg ctatttttgc agtgatatgt gatgttctgg gaagctcggc tggagagaag 120
tcgaaggaat gccagctgca catcaaggac atcttcagga agttcaggat tgccgtagct 180
aaactgaaaa ccaccatcca tggactctcc aaaccaaacg tgtttcttct cagcactaga 240
atctgtccac cagtgtttcc gtggaacatt caaaggattg gcacttatgc atgtttcccc 300
```

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agtttccata ttacagaata ccttgatagc atccaatttg catccttggt tagggtcaac 360
ccagtattct ccactcttga gttcaggatg gcagaatttc aggtctctgc agtttctagc 420
ggggttttta cgagaaccat caggactaat gaggctttct atttgtccat taacagactt 480
gagtgaagtc ataatctcat cggtgttgat tttgaaatcc attggttcat ctccataata 540
cggggcaaaa ccgccagctt tttcacctcc aatcccagca atggcagcgg ctccaacacc 600
accacagcaa ggaccagggg caccaggagg tccaggaggg cctggttgcc ctgggtggcc 660
tggggagccc tcagatcctc tttcacctct gttac
<210> 465
<211> 73
<212> DNA
<213> Homo sapiens
<400> 465
caggiccaga geteccaggi ticcaggity cagiccetce agicceagag eteccagggi 60
ttcggtttcc agt
                                                                73
<210> 466
<211> 507
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (507)
\langle 223 \rangle n = A,T,C or G
<400> 466
aagcatattg ctatacaaga ctttaaagac ttcataaaag ccaaacttgc agagtccctg 120
catggagtag ccaaggaaag teggageeea teetttagee aaaccaegaa caccateete 180
tttaagtgta actgagaatc cgttaaatat gcccttgtac ttttgggggt ccacctgcat 240
acggcatttc actaaatcca ggggaaccac agcagtgtgt gtcagaccac aacttaagac 300
cccaccaaag ccacacagtg cataatactt cgcggagcca aattcacaac tgtactcttc 360
cacggcggcg gctgccaggt tgcgagggcg gcggggctgg cccgtgggcc ctggggagct 420
gctgcggagg tccccgagac catcgtgcac canctgcaga tgtggcgtgt tgaaggggtt 480
cgcccgcgcc aggtgcgcca cggacga
                                                                507
<210> 467
<211> 183
<212> DNA
<213> Homo sapiens
<400> 467
cctcatgagc taccgggcca gctctgtact gaggctcacc gtctttgtag gggcctacac 60
cttctgagga gcaggagga gccaccctcc ctgcagctac cctagctgag gagcctgttg 120
tgaggggcag aatgagaaag gcaataaagg gagaaagaaa aaaaaaaaa aaaagggcgg 180
ccg
                                                                183
<210> 468
<211> 129
<212> DNA
<213> Homo sapiens
<220>
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<221> misc feature
<222> (1)...(129)
<223> n = A,T,C or G
<400> 468
geggeeget egaceggege egtegggene egggeeggge catggagetg tggaegtgte 60
tggccgcggc gctgctgttg ntgntgctgn tggtgcagtt gagccgcncn gccgagttct 120
acnccaang
<210> 469
<211> 243
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(243)
<223> n = A,T,C or G
<400> 469
gcggccgcgt cgacnggcca tggagactgt ggcacagtag actgtagtgt gaggctcgcg 60
ggggcagtgg ccatggaggc cgtgctgaac gagctggtgt ctgtggagga cctgctgaag 120
tttgaaaaga aatttcagtc tgagaaggca gcaggctcgg tgtccaagag cacgcagttt 180
gagtacgcct ggtgcctggt gcggagcaag tacaatgatg acatccgtaa aggcatcgtg 240
ctq
<210> 470
<211> 452
<212> DNA
<213> Homo sapiens
<400> 470
cctcaagtac gtccggcctg gtggtgggtt cgagcccaac ttcatgctct tcgagaagtg 60
cgaggtgaac ggtgcggggg cgcaccctct cttcgccttc ctgcgggagg ccctgccagc 120
teccagegae gaegeeaceg egettatgae egaceecaag eteateacet ggteteeggt 180
gtgtcgcaac gatgttgcct ggaactttga gaagttcctg gtgggccctg acggtgtgcc 240
cctacgcagg tacagccgcc gcttccagac cattgacatc gagcctgaca tcgaagccct 300
gctgtctcaa gggctcagct gtgcctaggg cgccctcct accccggctg cttggcagtt 360
gcagtgctgc tgtctcgggg gggttttcat ctatgagggt gtttcctcta aacctacgag 420
ggaggaacac ctgatcttac agaaaatacc ac
<210> 471
<211> 168
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(168)
<223> n = A,T,C or G
<400> 471
cttctccgct ccttctanga tctccgcctg gttcggnccg cctgcctcca ctcctgcctc 60
taccatgtcc atcagggtga cccagaagtc ctacaaggtg tccacctctg gcccccgggc 120
cttcagcagc cgctcctaca cgagtgggcc cggttcccgc atcagctc
```

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<210> 472
<211> 479
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(479)
<223> n = A, T, C \text{ or } G
<400> 472
gccaggcgtc cctctgtctg cccactcagt ggcaacaccc gggagctggt ttgtcctttg 60
tggagcctca ncagttccct ctttcanaac tcactgccaa gagccctgaa caggagccac 120
catgcagtgc ttcagcttca ttaagaccat gatgatcctc ttcaatttgc tcatctttct 180
gngtggcgca gccctgttgg cagcgggcat ctgggtgnca atcgatgggg catcctttct 240
gaagatette gggeeactgt egteeactge catgeagttt gteaacgngg getaetteet 300
categeagee ggegttgtgg tntttgetet tggttteetg ggetgetatg gtgetaanac 360
tgagagcaag tgtgccctcg tgacgntctt cttcatcctc ctcctcntct tcattgctga 420
ggntgcagnt gctgaggtcc gccttggtgt acaccacaat ggctgagccc ttnctgacn 479
<210> 473
<211> 69
<212> DNA
<213> Homo sapiens
<400> 473
gagcgatgga gcgtgggtag ggagggtcca cagtgtccac tcgccgtgtg cgaaggttga 60
ctcggtagt
<210> 474
<21.1> 155
<212> DNA
<213> Homo sapiens
<400> 474
gccgccactg ccgggagagc tcgatgggct tctcctgcgc gccgcccggt gtctggccga 60
gtccagagag ccgcggcgcc tcgttccgag gagccatcgc cgaagcccga ggccgggtcc 120
cgggttgggg actgcagggg aaggcagcgg tggcg
                                                                   155
<210> 475
<211> 282
<212> DNA
<213> Homo sapiens
<400> 475
ggcttcgacg ttggccctgt ctgcttcctg taaactccct ccatcccaac ctggctccct 60
cccacccaac caactttccc cccaacccgg aaacagacaa gcaacccaaa ctgaaccccc 120
tcaaaagcca aaaaatggga gacaatttca catggacttt ggaaaatatt tttttccttt 180
gcattcatct ctcaaactta gtttttatct ttgaccaacc gaacatgacc aaaaaccaaa 240
agtgcattca accttaccaa aaaaaaaaa aaagggcggc cg
<210> 476
<211> 434
<212> DNA
```

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<213> Homo sapiens
<400> 476
ctccaggaca gcgtccagct tggtgtcgtt gaagacgaag tggagcggat ggttgtagaa 60
acgagtgatg gtgctgagcg gcgtgcagtc ttcgggatcc acgaaggcca agtccttgag 120
gtagagcatg tccacgatgt tggagcgctc ctcctcgtac accgggatgc gcgtgtggcc 180
gctctgcatg atgctggcca ggacgccgaa gtccagcacg gtgctggcgt ccagcatgaa 240
gcagtcttcg aggggcgtga gcacgtcctc cacggtccgg cagcgcagca cgcccttgct 300
gagategetg taggggtege egeegeegeg egeeagetee ageaceeget eeegeageeg 360
cccgggccgc gccgccagct ccagcagctg ccccacgggc agcgcgacgg gcagagtgag 420
caggacggcc aggc
<210> 477
<211> 314
<212> DNA
<213> Homo sapiens
<400> 477
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gggcgtatga gtggggcgtg cgctccacgc ggaagtcgga gcctcctccc ctggataggg 120
tgtacgagat ccctggactg gagcccatca cctttgcggg gaagatgcac ttcgtgccct 180
ggctggcgcg gccgatcttt ccgccctggg accgcggcta caaggaccca aggttctacc 240
gctcgccccc tcttcacgag catccgctgt acaaagacca ggcctgctat atctttcacc 300
accettecce cctt
<210> 478
<211> 317
<212> DNA
<213> Homo sapiens
<400> 478
aacagagtga tcattccagt taagcggggc gaagagaata cagactatgt gaacgcatcc 60
tttattgatg gctaccggca gaaggactcc tatatcgcca gccagggccc tcttctccac 120
acaattgagg acttctggcg aatgatctgg gagtggaaat cctgctctat cgtgatgcta 180
acagaactgg aggagaggg ccaggagaag tgtgcccagt actggccatc tgatggactg 240
gtgtcctatg gagatattac agtggaactg aagaaggagg aggaatgtga gagctacacc 300
gtccgagacc tcctggt
                                                                   317
<210> 479
<211> 171
<212> DNA
<213> Homo sapiens
<400> 479
aggtgetttg ctagatgetg tgacaggtat gecaecaaca etgeteacag cetttetgag 60
gacaccagtg aaagaagcca cagctettet tggcgtattt atactcactg agtettaact 120
tttcaccagg ggtgctcacc tctgccccta ttgggagagg tcataaaatg t
                                                                  171
<210> 480
<211> 65
<212> DNA
<213> Homo sapiens
<400> 480
eccecagtgg aaggeteeca ecctggtaga tgaacageec etggagaact acctggatat 60
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```
ggagt
                                                                   65
<210> 481
<211> 207
<212> DNA
<213> Homo sapiens
<400> 481
cacagcgtgc tctgcggggt cactcccact ttgttagtga tgtggttatc tcctcagatg 60
gccagtttgc cctctcaggc tcctgggatg gaaccctgcg cctctgggat ctcacaacgg 120
gcaccaccac gaggcgattt gtgggccata ccaaggatgt gctgagtgtg gccttctcct 180
ctgacaaccg gcagattgtc tctggat
<210> 482
<211> 319
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(319)
<223> n = A, T, C or G
<400> 482
cacactgtgc cettecagtt getggeeegg tacaaaggee tgaaceteae egaggatace 60
tacaageece ggatttacae etegeecace tggagtgeet ttgtgacaga cagtteetgg 120
agtgcaegga agtcaeaact ggtctateag teeagaeggg ggeetttggt caaatattet 180
totgattact tocaagoooc ctotgactac agatactace cotaccagtg ottocaaact 240
gcacaacacc cnagettnet ettecagnae aagagggtgt cetggteest ggcctacete 300
cccaccatcc agagetget
<210> 483
<211> 233
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(279)
<223> n = A,T,C or G
<400> 483
acaggcccag tggcgcctag ccttcagctg ctgggctctc ccgagcctgc cttagcccat 60
acaaccactt gatcacgegg gcattgcgct ccaccaccga cacgccatag ggaacgcqct 120
cccgggcccg ctcctcaaca gtcaccgagc tgcggcggga gcagccccct tcagagctgc 180
ccggcccagc actgggccct gccagggaca cnatatccga gctggcccgt gcc
<210> 484
<211> 194
<212> DNA
<213> Homo sapiens
<400> 484
agagcccttg ctggggggtg cctgggagat ggggtaagaa gagctttcat ttgtctggta 60
gatagatagc atgtaagggg gtggttgtcc caggaggcag ctgctgacag gtttgctaca 120
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cacageceeg tgtgcccetg		cctgggtgct	cattcagaga	ggggctatca	tctgggagcc	180 194
<210> 485 <211> 67 <212> DNA <213> Homo	sapiens					
<400> 485 tccatatcca gggaagt	ggtagttctc	caggggctgt	tcatctacca	gggtgggagc	ctcccactgg	60 67
<210> 486 <211> 70 <212> DNA <213> Homo	sapiens					
<400> 486 taccgagtca atcgctcagt	accttcgcac	acggcgagtg	gacactgtgg	accctcccta	cccacgctcc	60 70